



# ACTA MEDICA SCANDINAVICA

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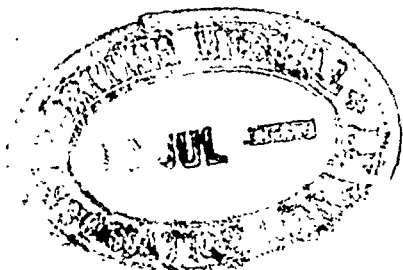
IN HOLLANDIA: F. S. P. van Buchem, J. Mulder.

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From the Medical Department at the Chr. Michelsen Institute, Bergen, Norway. (Chief: Konrad Birkhaug, M. Sc., M. D., F. A. C. P.)



## Hematological studies in tuberculosis.

Variations in the Blood Cells of Guinea Pigs inoculated Intracutaneously or Percutaneously with BCG Vaccine.

By

KONRAD BIRKHAUG and HALFDAN SCHJELDERUP.

(Submitted for publication December 6, 1944).

In our 1944 comparative experimental investigation on the »Protective Value of the Intracutaneous and Percutaneous Methods of BCG Vaccination» (1), we concluded that Rosenthal's multiple puncture (2), Weill-Hallé's scarification (3) and Wallgren's intracutaneous (4) BCG vaccination methods, each is capable of producing a significant relative resistance against a virulent tuberculous infection. On further bacterio-pathological examinations, we decided that Rosenthal's multiple puncture method stimulated the most rapid allergy and potent tuberculosis resistance. The present hematological study on these variously immunized and subsequently infected animals was undertaken as *intra vitam* control on the progress of the tuberculous disease.

Earlier studies on blood cells in experimental and clinical tuberculosis (5) clearly emphasize that »the blood picture in tuberculosis can hardly be said to be pathognomonic, but should be of considerable aid in diagnosis. However, its greatest service is in prognosis, since the quantitative abnormal changes in the cells are progressive with advancing disease.» Our repeated reviews of



this literature should make it unnecessary to reiterate the importance of hematology in tuberculosis. On the other hand, we shall briefly connect the present study with its previous experimental data (1).

### Materials and methods.

Forty-eight normal and tuberculin negative albino guinea pigs, weighing between 454 and 485 gms, were divided into four equal groups, each containing 6 male and 6 female animals. Three groups were epilated in the right lumbo-sacral region with a paste made up of equal parts of barium sulphite and wheat flour mixed with water. The skin was afterwards thoroughly washed with lukewarm water. Vaccination with BCG took place the following day. The vaccine was freshly prepared from a 3 weeks old Sauton culture film and was made to contain 20 mg BCG per ml for the multiple puncture and scarification methods and 0.5 mg per ml for the intracutaneous injection. These doses are identical with the concentrations of BCG employed on man.

The *multiple puncture* group was given a total of 40 punctures with our 8-needled apparatus pressed heavily against the skin previously moistened with the 20 mg/ml vaccine emulsion. An interspace of 3—4 mm was allowed between each of the 5 rows of punctures. After vaccination a few drops of the vaccine emulsion were spread over the punctured area and a sterile tissue paper covered this area in order to retain the moisture in approximately 5 minutes. The paper was then removed and no extra bandage was applied to the vaccinated area.

The *scarified* group of animals was prepared in the same manner except that 5 lines of approximately 4 cm's length and 3—5 mm apart were made with the vaccination lancet pressed hard against the skin, in the manner of the Pirquet tuberculin test.

The *intracutaneous* group of animals was injected with 0.1 ml BCG vaccine containing 0.5 mg/ml. The injection was made slowly in the uppermost layer of the epidermis so as to form an elevated papule in the middle of the epilated area.

### Post-vaccination Reactions.

The inflammatory vaccination reactions increased steadily during the first week until the multiple puncture papules and the scars measured 2—4 mm in width and 1—2 mm in height while the intracutaneous vaccination site became palpably indurated. Approximately 3 weeks after vaccination, the inflammatory reactions began to fade in the scarified animals while they persisted in the multiple puncture papules. The ensuing cold abscess in the intracutaneous group invariably perforated during the third and fourth week. Complete resorption and healing of the vaccination lesions occurred approximately 40 days after vaccination. The axillary and inguinal glands on the vaccinated side became palpably enlarged and firm during the first month after vaccination and remained hypertrophied, especially in the multiple puncture group, for as long as 4—5 months after vaccination.

The development of allergy was determined by injecting 10 mg tuberculin intradermally in all the vaccinated animals. Already 3 weeks after vaccination 100 percent of the multiple puncture group reacted intensely with induration and erythema. The scarified and intracutaneous groups gave 100 percent positive tuberculin reactions first 8 weeks after vaccination.

Fifty-eight days after vaccination when all the animals had become allergic, all the vaccinated animals and the control group were inoculated *intraperitoneally* with 0.000.1 mg of a highly virulent strain of human tubercle bacilli («Tuxen»). This dose gave rise to 1283 eugonic colonies on Löwenstein's egg medium in the course of 10 weeks incubation. We may infer therefore that each animal received approximately 1300 viable and virulent tubercle bacilli. The intraperitoneal inoculation route was chosen in order to avoid unnecessary suppuration from the inoculated site during the blood work manipulations, which is always the case following the subcutaneous inoculation in the hind leg. It should be borne in mind that the intraperitoneal inoculation with virulent tubercle bacilli entails a more rapid absorption and spread of the bacilli than does the subcutaneous inoculation which produces a slower progression of ensuing tuberculous lesions, in accordance with the law of Cohnheim. The intraperitoneal inoculation presents therefore a greater tax on the protective mechanism in the immunized animals than does the subcutaneous inoculation.

## Post-infection Reactions.

The intracutaneous tuberculin test with 10 mg tuberculin was made on all the four groups of animals 8 weeks after the virulent inoculation. All the animals gave positive reactions. The control group reacted most intensely with an average induration measuring 2154 mm<sup>3</sup> and central necrosis measuring 312 mm<sup>2</sup>. The vaccinated groups reacted less intensely and extensively. Thus the scarified group reacted with 1712 mm<sup>3</sup> induration and 194 mm<sup>2</sup> central necrosis, the intracutaneous group respectively with 1526 mm<sup>3</sup> and 168 mm<sup>2</sup> and the multiple puncture group with 1394 mm<sup>3</sup> and 121 mm<sup>2</sup>. If we suppose that the intensity of the tuberculin reactions mirrors the succession of events associated with visceral tubercle formation through successive stages of bacteriostasis and other immune mechanical barrier influences produced by the immunization with BCG, then by comparing the control group tuberculin reactions with the immunized group reactions, it does appear as if the tuberculous infection proceeded most slowly in the multiple puncture group, a little more rapidly in the intracutaneous group and still more rapidly in the scarified group.

Our presupposition was verified at autopsy of the eight control animals (66.7 percent) which succumbed with generalized tuberculosis between the sixty-eight and one-hundred-and-second day after the virulent inoculation, of two intracutaneous animals (16.7 percent) and one scarified animal (8.3 percent) which also died of generalized tuberculosis 101—108 days after the virulent inoculation. None of the multiple puncture animals had died spontaneously up to this time.

All the surviving animals were killed 103—110 days after the virulent inoculation in order to make a comparable quantitative assessment of the degree of tuberculosis within each group. The macroscopic scoring of tuberculous involvement in the vaccinated and control animals, as well as the exact quantitative assessment of the volume and weight of individual organs and glands, subsequently treated statistically, brought further verification of our presupposition. The multiple puncture group presented the smallest degree of tuberculous lesions, the scarification and intracutaneous groups still more tuberculosis while the control group showed

excessively greater tuberculous lesions than the BCG-immunized groups. Bacterial cultures of the homogenized spleen from the vaccinated and control animals revealed per 0.002 g splenic tissue 0.3 tubercle bacillus in the multiple puncture group, 2.5 bacilli in the intracutaneous group, 3.5 bacilli in the scarification group and 50.1 bacilli in the control group.

These striking immunizing effects of the 3 parenteral methods of BCG-vaccination gave 100 percent significant deviations from the control quantitative data in every one of the vaccinated groups. By fine-combing the quotients of probable error (*t*) for each of the vaccinated groups, it was apparent that the multiple puncture group scored a slightly higher protection against the virulent superinfection than the scarification and intracutaneous groups. But the essential fact remains that any one of the parenteral BCG-vaccination methods yielded deviations from the unprotected control group which were larger than 3 times their probable error and as such of undisputed statistical significance. It now remains to be seen if the present hematological study of each type of white blood cell, the monocyte-lymphocyte and neutrophile-lymphocyte ratios and the leukocytic index in each of the four groups of animals will substantiate the post-mortem findings.

### Hematological investigation.

The normal base-line values for total white cells, each type of cells or cellular ratios or combinations, were made on the basis of 12 animals in each of the four groups under discussion. The assessment of the bi-weekly deviations in the blood cells from the established normal base-line values, was not done on the basis of a common normal value for all the groups, but on the basis of the pre-vaccination values obtained in each particular animal group. Complete white cell counts were made 2 and 5 weeks after the parenteral BCG-vaccination and every other week after the virulent superinfection until the experiment was terminated 14 weeks later. Thus the entire hematological investigation comprises 480 total and 480 differential white cell counts.

Enumeration of the total white cells was done after the Ellermann dilution principle, making use of standardized separate pi-

ettes for blood and diluting fluids, the mixture taking place in special diluting tubes. The cells were always counted within 6 hours after the blood was drawn. Standardized green glass Levy quadruple counting chambers were employed for the total white cell counts. We adhered strictly to the rule of counting 10 large squares, each measuring 1 mm<sup>2</sup>.

The dry blood film was fixed for 3 minutes with the methyl alcohol contained in the May-Grünwald stain. Then equal parts of distilled water are added and the staining process is continued for 1 minute. The stain is now decanted and excess fluid is removed by touching the edge of the slide to a filter-paper. The film is now stained for 15 minutes with diluted Giemsa stain (15 drops of stain mixed with 10 ml distilled water) and thereafter washed with distilled water and is blotted dry. Each author has counted 100 differential cells in each smear. Whenever 2 counts have showed excessive divergence, we have continued to count up to 600 cells.

As in our previous investigations in tuberculosis, we have made use of Fisher's (6) statistics to determine if two samples differ significantly in their mean values or belong to the same population. The significance of deviations in each type of white cell or cellular ratio was decided by calculating deviations from the normal base-line value and their probable error and then dividing the former by the latter. The obtained *t quotient* expresses the deviation as a multiple of its probable error. The statistical significance *P* (probability) of various values of such quotients is stated in Fisher and Yates' (7) table III. In the present study we have rejected as insignificant any mean value of *P* in excess of 0.01. The symbol  $P \leq 0.01$  signifies, therefore, that the observed mean deviations bearing this or smaller values must be considered to represent *an absolute statistical significance* which cannot have occurred by chance alone (8). In Fisher and Yates' table III for distribution of *t* we find that a  $P \leq 0.01$  requires that  $t \geq 2.819$  for 24 counts or samples which in our case are composed of 12 normal base-line and 12 post-inoculation samples. Every difference having *absolute significance* is italicised in Table 1.

## Results.

*Total white blood cells:* — In Table 1 it is seen that the total white cells in the multiple puncture group made significant deviations from the normal base-line value in the seventh, ninth, eleventh and thirteenth post-inoculation weeks and always in an increasing direction. This gives the total white cell count an efficiency of 57 percent in this group of animals. The scarified group made likewise significant abnormal deviations in an increasing direction during the first, eleventh and thirteenth post-inoculation total white cell counts, or an efficiency of 43 percent for this group of animals. The intracutaneous group did likewise continually between the fifth and thirteenth post-inoculation weeks, or an efficiency of 71 percent while the control group presented increasing significant abnormal deviations in the total white cells in the first, ninth and thirteenth weeks, or an efficiency of 43 percent. Chart 1 presents these mean deviations in the total white cells as multiples of their probable error. The odds against occurrence by chance are small in the case of all points falling in the shaded zone and their significance is not certain. But the odds against occurrence by chance are high in the case of deviations falling outside the shaded zone; such deviations are considered significant. The horizontal line in the center of the shaded zone represents the normal value; the direction of each deviation from the normal is shown.

*Eosinophiles:* — In Table 1 it is seen that the normal base-lines for eosinophiles are higher than normal in all the four groups of animals. We are unable to explain the eosinophilia and regret that the war-time restrictions made it impossible to exchange the eosinophilic animals for normal ones, as we have done on previous occasions. Otherwise the animals were in excellent health when the experiment was begun.

In Table 1 and Chart 2 we observe that the multiple puncture group made no significant abnormal deviations in the eosinophiles. The scarified group made only one significant abnormal deviation in the fifth post-inoculation week and in a decreasing direction, or an efficiency of 14 percent. The intracutaneous group made two significant abnormal deviations in a decreasing direction in the fifth and thirteenth post-inoculation weeks, or an efficiency of 29

Table 1.

Mean ante-inoculation, post-vaccination and post-infection bi-weekly values for each type of leukocytes, for the monocyte-lymphocyte and neutrophile-lymphocyte ratios and leukocytic index in each of the four groups of animals.

	Animals	Baseline	Post-vaccination		Post-infection							
			2 Wks.	5 Wks.	1 Wk.	3 Wks.	5 Wks.	7 Wks.	9 Wks.	11 Wks.	13 Wks.	
White blood cells	MP	11,680	12,400	11,380	14,000	14,480	12,760	14,800	15,440	16,950	15,590	
	SC	12,280	12,200	11,310	15,040	14,680	14,150	14,000	15,360	15,270	14,550	
	IC	12,420	13,280	10,900	14,630	14,500	19,410	18,000	18,830	19,820	21,860	
	C	12,030	12,590	10,670	16,280	15,000	14,710	14,800	16,930	13,700	21,300	
Eosinophiles	MP	11.8	14.0	18.7	16.1	13.7	13.8	15.7	13.9	15.2	12.7	
	SC	17.2	17.6	21.4	17.7	9.7	9.1	13.4	16.6	11.5	10.3	
	IC	22.2	23.0	24.4	20.5	16.8	11.6	15.6	16.5	14.9	10.6	
	C	17.2	27.8	29.5	31.8	10.7	12.5	15.0	14.4	11.4	6.5	
Basophiles	MP	0.5	0.2	0.4	0.5	0.3	1.1	0.4	0.8	0.5	0.9	
	SC	0.4	0.4	0.5	0.5	0.8	0.5	0.4	1.0	0.9	0.7	
	IC	0.5	0.6	0.8	0.5	0.3	0.2	0.5	0.5	1.1	1.0	
	C	0.7	0.6	1.0	1.2	0.8	0.8	1.7	1.0	0.8	0.8	
Stab cells	MP	1.9	1.3	0.8	0.8	1.1	1.0	0.1	0.8	0.3	0.2	
	SC	1.6	1.3	1.3	0.9	1.4	0.4	0.4	1.1	0.5	0.8	
	IC	2.0	1.3	1.0	1.0	1.2	0.2	0.7	0.3	0.6	0.4	
	C	1.8	1.3	0.8	1.0	1.8	1.5	1.0	0.8	2.1	2.8	
Segmented cells	MP	37.8	37.4	36.5	37.0	38.7	39.4	42.2	43.3	41.3	38.7	
	SC	36.3	32.5	32.6	37.3	37.5	48.4	39.7	38.2	42.7	43.4	
	IC	34.6	27.7	28.1	31.5	37.5	59.5	39.5	36.2	40.0	44.9	

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Lymphocytes	MP	46.1	42.5	41.5	42.8	42.8	42.2	38.5	37.3	39.7	44.5
	SC	50.6	46.3	45.0	41.3	45.3	46.1	42.5	36.9	36.8	40.0
	IC	39.0	45.6	44.2	43.5	40.7	33.5	40.3	39.5	37.5	37.1
	C	34.5	34.1	30.3	33.8	25.3	24.5	26.9	26.0	27.5	29.5
Monocytes	MC	2.5	3.0	1.9	2.6	3.3	3.0	3.0	3.9	3.0	2.9
	SC	2.5	1.9	1.6	2.0	5.2	3.4	3.5	6.1	6.0	4.7
	IC	1.9	1.8	2.2	1.8	3.5	5.0	3.3	6.8	7.4	5.5
	C	2.9	2.2	1.8	2.6	12.3	11.0	8.9	10.9	15.7	15.0
Monocyte-lymphocyte ratio	MP	0.054	0.074	0.048	0.067	0.082	0.077	0.084	0.116	0.082	0.068
	SC	0.068	0.040	0.037	0.060	0.124	0.125	0.085	0.167	0.189	0.150
	IC	0.052	0.045	0.049	0.043	0.038	0.148	0.083	0.202	0.158	0.254
	C	0.088	0.070	0.081	0.090	0.539	0.459	0.354	0.469	0.584	0.554
Neutrophile-lymphocyte ratio	MP	0.916	0.955	0.960	0.966	1.032	0.972	1.118	1.275	1.136	0.909
	SC	0.954	0.754	0.788	1.104	0.961	0.906	0.998	1.129	1.319	1.246
	IC	0.996	0.702	0.757	0.797	0.985	1.595	1.027	1.050	1.140	1.707
	C	1.416	1.114	1.498	1.033	2.409	2.495	1.976	2.031	1.876	2.019
Leukocyte index	MP	7	8	7	11	13	11	16	16	17	13
	SC	9	5	3	15	13	9	11	15	20	19
	IC	10	9	4	11	11	22	14	19	18	18
	C	14	11	12	16	34	36	30	34	37	37

Note: Statistically significant deviations from the ante-inoculation base-line appear in italics. Values shown in ordinary type proved not to be statistically significant deviations from the ante-inoculation base-line.

MP = multiple puncture. SC = scarification. IC = intracutaneous. C = control.



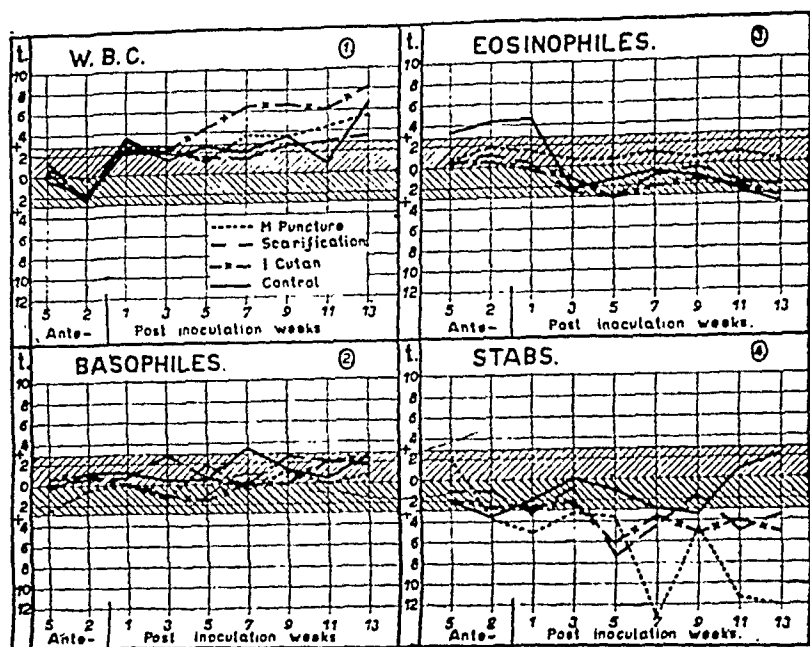
percent. The control group made one significant increasing deviation in the fifth week and one decreasing significant deviation in the thirteenth week, or an efficiency of 14 percent in each direction. It is apparent, however, that the decreasing tendency in the eosinophiles was dominant in the control group, although these decreases failed to score significant dimensions except in the very last week.

*Basophiles.* — No significant abnormal deviations in the basophiles were made in the multiple puncture and intracutaneous groups. One significant increasing deviation occurred in the scarified group in the third week and one in the control group in the seventh week, or each of these two groups giving an efficiency of 14 percent for the basophiles, as shown in Chart 3.

*Stab cells:* — It is noted in Table 1 that the mean bi-weekly values for stab cells in the four group of animals fluctuate very little and with one exception in a decreasing direction. In our previous hematological studies (5) we observed 25 percent efficient increases in the stab cells during the progressive tuberculous infection in the control animals. In our present study we observe that the multiple puncture group made 100 percent efficient decreasing deviations in the stab cells, the intracutaneous group made 86 percent efficient decreases, the scarified group 71 percent and the control group 29 percent. But these significant decreases are much less reliable than might be indicated without comparing these with the excessively small fluctuations in the mean stab cell counts in Table 1.

*Segmented cells:* — As shown in Table 1, the segmented cells made no significant abnormal deviations in the multiple puncture group and only one increasing abnormal deviation in each of the scarified and intracutaneous groups and one decreasing significant deviation in the control group. Chart 5 shows these 14 percent efficiencies of the segmented cells in each of the four groups.

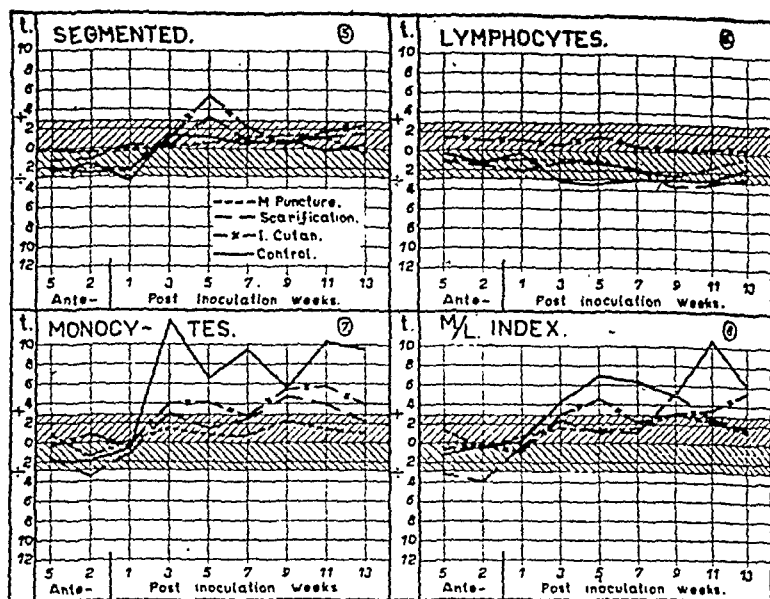
*Lymphocytes:* — In the multiple puncture and intracutaneous groups we failed to observe any significant abnormal deviations in the lymphocytes during the post-inoculation period. In the scarified group two significant decreasing deviations from the normal lymphocyte value occurred in the ninth and eleventh weeks, or an efficiency of 29 percent. In the control group we observed five significant decreasing deviations in the third, fifth, seventh, ninth and eleventh post-inoculation weeks, or an efficiency of 71 percent. Here



Charts 1—4. Bi-weekly mean deviations of (1) total white cells, (2) eosinophiles, (3) basophiles and (4) stab cells, expressed as multiples of their probable error.

we find a fair agreement with our previous findings (5) that the decreasing lymphocyte percentages reflect more faithfully the decline in resistance during tuberculous disease than any of the abovementioned individual blood cells (Table 1 and Chart 6).

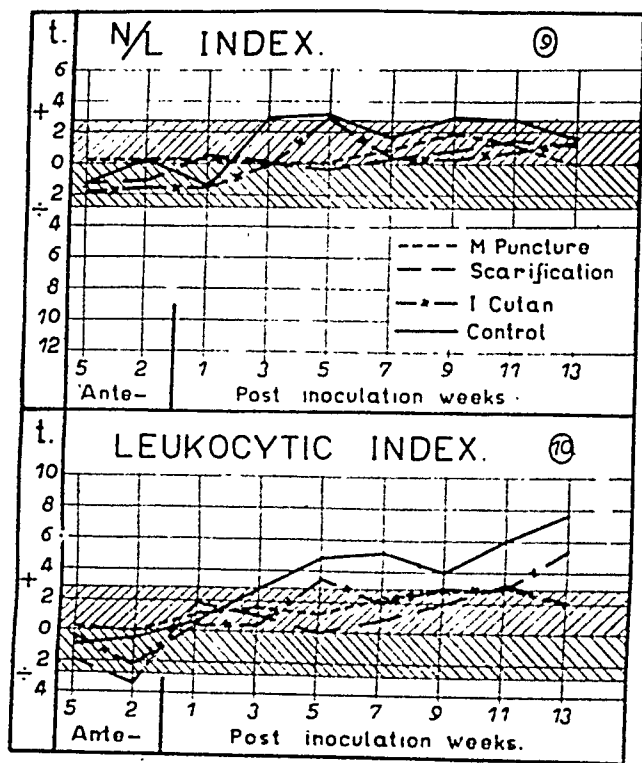
*Monocytes:* — The multiple puncture group presented no significant abnormal deviations in the monocytes during the entire post-inoculation period. The scarified group showed three significant abnormally increasing deviations of monocytes in the third, ninth and eleventh post-inoculation weeks, or an efficiency of 43 percent. The intracutaneous group presented five significant abnormally increasing deviations in the monocytes in the third, fifth, ninth, eleventh and thirteenth post-inoculation weeks, or an efficiency of 71 percent. The control group presented 6 significant increases out of 7 post-inoculation monocyte counts from the third week until the end of the experiment, or an efficiency of 86 percent. Thus the monocyte proved to be more sensitive than the lymphocyte in reflecting the progressive trend in the tuberculous disease. This confirms the findings mentioned earlier of Florence R. Sabin and her co-workers as well as our own studies (5) (Chart 7).



Charts 5—8. Bi-weekly mean deviations of (5) segmented cells, (6) lymphocytes, (7) monocytes and (8) monocyte-lymphocyte ratio, expressed as multiples of their probable error.

*Monocyte-lymphocyte (M/L) ratio:* --- One significant increasing abnormal deviation in the M/L ratio was observed in each of the multiple puncture and scarified groups in the ninth post-inoculation week, or an efficiency of 14 percent for each group. The intracutaneous group presented five significant increasing abnormal deviations in the M/L ratio in the third, fifth, ninth, eleventh and thirteenth post-inoculation weeks, or an efficiency of 71 percent. The control group made six significant increasing deviations from the third post-inoculation week until the end of the experiment, or an efficiency of 86 percent. These findings are in fair agreement with earlier blood studies in tuberculosis (5) and prove that the M/L ratio competes with the monocyte as the most reliable detectors of progressive tuberculous disease.

*Neutrophile-lymphocyte (N/L) ratio:* — The multiple puncture and scarified groups failed to show any significant abnormal deviations in the N/L ratio during the post-inoculation period. The intracutaneous group showed only one such significant increasing deviation in the fifth week, or an efficiency of 14 percent. The control group, on the other hand, presented four significant



Charts 9—10. Bi-weekly mean deviations of (9) neutrophile-lymphocyte ratio and (10) leukocytic index, expressed as multiples of their probable error.

increasing deviations in the third, fifth, ninth and eleventh post-inoculation weeks, or an efficiency of 57 percent (Chart 9).

*Leukocytic index (L. I.):* — The L. I. was proposed in 1935 by Crawford and Medlar (9). It «equals the value of the neutrophile-lymphocyte percentage ratio plus the value of the elevation of the monocytes plus the value of the abnormal total white cell count.» The significance of these four variables has been pointed out by Medlar (10), namely,

1. The neutrophile plays the chief rôle in tuberculous abscess-formation and in the extension of tuberculous ulcers.
2. The lymphocyte predominates when the tuberculous lesion is healing.
3. The mononuclear leukocyte is the chief cell of new tubercle formation.
4. The total leukocyte counts by themselves roughly indicate the volume of deranged tissue with which the leukocytes have to cope.

On the basis of extensive clinical studies on selected groups of tuberculous cases, Medlar attaches the following prognostic interpretation to the leukocytic index, namely: »0 to 15 = ideal increasing favorable; 16 to 20 = slightly favorable; 21 to 26 = slightly unfavorable; 27 to 35 = unfavorable, and 36 and over = increasingly very unfavorable.» The reader is referred to Crawford's original paper (9) for the use of a handy calculator which facilitates the computation of the leukocytic index. Since 1937 we have constantly made use of the L. I. in our blood studies in tuberculosis. In these we have with satisfaction confirmed Medlar's conclusion that the L. I. »does indicate the trend of the underlying pathological process in tuberculosis.»

The multiple puncture and scarified groups presented each one significant increasing deviation in the L. I. in the eleventh post inoculation week, or an efficiency of 14 percent. The intracutaneous group scored four significant increasing deviations in the fifth, ninth, eleventh and thirteenth weeks, or an efficiency of 57 percent. The control group followed the scoring of the monocytes and the monocyte-lymphocyte ratio by presenting six significant increasing deviations in the leukocytic index out of seven post inoculation counts, or an efficiency of 86 percent. Thus, the monocytes, the monocyte lymphocyte ratio and the leukocytic index represent the three most reliable tests which reflect the progressive trend in tuberculous disease.

### Discussion.

It would seem needless in this place to recapitulate our opinion on the significance of hematology in experimental and clinical tuberculosis. We agree with Smithburn, Sabin and Hummel (5) when they state that »while the blood picture can hardly be said to be pathognomonic, it should be of considerable aid in diagnosis. But perhaps its greatest value is in prognosis, since the quantitative changes in the cells are progressive with advancing disease.» In our control tuberculous animals we have again reconfirmed the verity in this statement in respect to the high scoring of efficiencies in the abnormal deviations of the monocytes, the monocyte lymphocyte ratio and the leukocytic index in reflecting

Table 2.

*Percent Efficiencies of Blood Cells and Cellular Ratios in showing abnormal Values in variously BCG-Vaccinated and Control Animals infected with virulent Tubercle Bacilli.*

	Multiple puncture	Scarifi- cation	Intracu- taneous	Control
Monocytes .....	0	43	71	86
Ratio monocytes/lymphocytes ....	14	14	71	86
Leukocytic Index .....	14	14	57	86
Lymphocytes .....	0	29	0	71
Ratio neutrophils/lymphocytes ....	0	0	14	57
Total white cells .....	57	43	71	43
Eosinophiles .....	0	14 <sup>1</sup>	29 <sup>1</sup>	29 <sup>1</sup>
Stab cells .....	100 <sup>2</sup>	71 <sup>2</sup>	86 <sup>2</sup>	29 <sup>2</sup>
Segmented cells .....	0	14	14	14
Basophiles .....	0	14	0	14

<sup>1</sup> Data open to question as base-line values were higher than normal.

<sup>2</sup> Less reliable than might be indicated, since we are dealing with very small percentages (not surpassing 2.8 percent).

reliably the underlying pathological processes. By contrasting the abnormal deviations in the blood cells in each of the variously BCG-vaccinated and subsequently superinfected animals with those obtained in the unprotected control animals, we may be able to discern differences in the degree of resistance towards the progress of the virulent infection which might shed light on the most effective method of artificial specific immunization. For this purpose we have summarized the efficiencies scored by the blood cells or combination of cells in the four groups of animals (Table 2).

The significant deviations in stab cells are of such small degrees that they are less reliable than indicated. We may therefore eliminate this type of cell from the discussion.

Using the control group blood changes as prototypes for those occurring in generalized and fulminating tuberculous disease, we observe that the monocytes top the list of individual cells which are abnormally stimulated into activity in tuberculosis. The control group make a showing of 86 percent significant abnormal deviations in the monocytes, the intracutaneous group 71 percent, the scarified group 43 percent while the multiple puncture group remains unaffected. If we should alone choose the monocytes as the arbiter to

Table 3.

*Percent Efficiencies of Blood Cells and Cellular Ratios in showing abnormal Values in Tuberculosis.*

	Birkhaug 1942 (1)	Birkhaug & Schjelderup		Smith- burn & al. 1937 (4)
		1943 (2)	1944 (3)	
Leukocytic Index .....	91	100	86	—
Ratio monocytes/lymphocytes ..	91	88	86	89
Monocytes .....	91	88	86	79
Lymphocytes .....	73	63	71	74
Ratio neutrophiles/lymphocytes	64	50	57	58
Total white cells .....	64	63	43	37 <sup>2</sup>
Neutrophiles .....	27	50	43	42 <sup>2</sup>
Eosinophiles .....	0	0	29 <sup>3</sup>	42
Basophiles .....	0	0	14	53 <sup>1</sup>

Series (1) Acta Med. Scand., 1942, 110, 201; (2) Ibid., 1943, 113, 527; (3) our present article, and (4) Amer. Rev. Tuberc., 1937, 36, 673.

<sup>1</sup> »Data open to question since base-line values were lower than those of Casey & Pearce (J. Exper. Med., 1930, 51, 83) and Thomas (Ibid., 1936, 64, 97, table 4). Animals may have shown rise in basophiles due to influence of state of maturity.»

<sup>2</sup> »Less reliable than might be indicated, since some values were high and others low, indicating that both determinations are subject to variation from a variety of causes, such as tuberculosis of bone marrow, secondary infections, etc.»

<sup>3</sup> Data open to question as base-line values were higher than normal.

settle the dispute about the BCG-immunization method *par excellence*, we would be forced to admit the multiple puncture method to the first place, the scarified group to the second place and the intracutaneous group to the third place. This decision would agree well with the findings already scored by the macroscopic pathological examination (1) of visceral tuberculous changes in the four groups of animals under discussion.

While the monocytes prove to be more sensitive to tuberculous infection than the lymphocytes and appear earlier in increasing numbers in the peripheral blood than the lymphocytes, it is nevertheless conceded that the retarded decline in lymphocytes more properly indicates a lowered individual resistance towards advancing tuberculous disease than any other individual blood cell type. Thus it is interesting to note the 29 percent efficient decline in

lymphocytes in the intracutaneous group and none whatsoever in the multiple puncture and scarified groups while the control group scored 71 percent significant decline in the lymphocytes. Likewise, the intracutaneous group scores the highest abnormal efficiencies in the total white cells, neutrophile-lymphocyte ratio and eosinophiles next after the control group. These excessive abnormal changes in the blood picture in the intracutaneous group must necessarily be interpreted to mean that the resistance against virulent tubercle bacilli was slightly less in this group than in the scarified group and that the multiple puncture group possessed the greatest resistance.

In Table 3 we have connected together our 1942, 1943 and present significant abnormal deviations in the blood picture in experimental tuberculosis as well as the findings by Smithburn, Sabin and Hummel in tuberculous rabbits. It will be seen that there exists a remarkable correlation between the order of significant blood changes taking place during advancing tuberculous disease. This fact adds strength to our deduction from the present study that every one of the three parenteral BCG immunization methods is capable of retarding the changes in the blood picture which characterize progressive tuberculous disease. But the most effective retardation of the tuberculous blood picture takes place in the animals immunized by the BCG multiple puncture method.

Thus we have proved that the abnormal changes in the blood picture, especially in the augmented monocytes, monocyte-lymphocyte ratio and leukocytic index, reliably register the trend of the underlying pathological processes in tuberculosis.

### Summary.

For the purpose of discerning variations in the degree of specific acquired resistance against a virulent tuberculous infection, a hematological study is made on comparable groups of guinea pigs immunized with BCG by Rosenthal's multiple puncture, Weill Hallé's scarification and Wallgren's intracutaneous vaccination methods.

The non-vaccinated and similarly infected control guinea pigs revealed that the significant abnormal deviations in monocytes, monocyte-lymphocyte ratio and leukocytic index of neutrophiles,



lymphocytes, monocytes and total white cells, register most accurately the advancing tuberculous disease.

The blood picture in the animals immunized with BCG parenterally and superinfected with virulent tubercle bacilli, revealed a significantly retarded abnormal deviation in the monocytes, monocyte-lymphocyte ratio and leukocytic index. The multiple puncture BCG vaccination method, however, produced a slightly more retarded abnormal blood picture than the scarification and intracutaneous BCG vaccination methods.

The hematological study substantiates the pathological data on the same groups of animals to the effect that the parenteral BCG vaccination produces a relatively significant resistance against a virulent tuberculous infection.

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The authors wish to express their appreciation of the technical and statistical assistance of Mr. Sigbjørn Aamodt.

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(From the department for nervous and mental disorders at »Filadelfia» Dianalund, Denmark. Chief Physician: H. I. Schou, M. D.)

## The effect of insulin coma and the awakening from it on the amino acid-N in plasma.

By

CARSTEN TROLLE.

(Submitted for publication October 27, 1944).

Even small contributions to elucidate the way in which the nitrogen metabolism is influenced by the hormones may be of interest and I shall therefore give some results for the hypoaminoacidemia obtained in human beings during an insulin shock treatment for mental disease. Most investigators are agreed that insulin injections lower the blood amino acid nitrogen (Farr and Alpert, 1940, and Crismon, Hanvey and Luck, 1940). The results given here seem to be of further interest as it is found that the awakening of the patients from insulin precoma or coma by either saccharose dissolved in water and given per stomach tube or by intravenous injections of glucose dissolved in water causes a further fall in amino acid-N in plasma.

Technique: The amino acid-N was determined by the gasometric nitreous acid method of Van Slyke, 1929. The insulin was obtained from »Novo» Copenhagen. The insulin treatment was performed as described in the report from the Danish Psychiatric Society, 1942.

Before I give the tabel I shall point out that the values between which the amino acid-N varies in normal fasting subjects are found to lie between 4.5 and 8.1 (Kirk, 1936) and between 4.2 and 6.0 (Schou and Trolle, 1944). The insulin treatments were performed in the morning and the patients were not allowed to take any food previously.

Pt.	Sex	Age years	Date	Amount of insulin injected Internat units	The amino acid-N		
					before insulin injection	in precoma	in coma
A. F.	♀	50	17/10-40	72			2.7
—	—	—	4/11-40	72			3.1
S. C.	♀	44	22/11-40	48			4.0
M. H.	♀	25	9/1-41	176			2.5
—	—	—	10/1 -41	186			2.9
H. R.	♂	30	17/10-40	240		3.2	3.1
—	—	—	25/10-40	256			3.3
—	—	—	4/12-40	312	5.0	3.9	4.6
—	—	—	10/12-40	304			4.5
K. G. N.	♂	27	25/10-40	320			4.1
—	—	—	31/10-40	312			3.
—	—	—	22/11-40	272			2
—	—	—	2/12-40	272			2.5
—	—	—	6/12-40	248	6.3	4.8	3.8
—	—	—	10/12-40	240			
A. Q.	♂	26	10/22-40	208	6.7	5.4	
R. J. M.	♀	21	1/2 -41	144			3.0
M. C.	♀	32	11/2 -41	56			3.

During insulin treatment.

plasma in mg %		with saccha- rose dissol- ved in water (per os). Amount and per cent	Diagnosis	In insulin treatment from Date
	after awakening			
			Schizophrenia paranoides	3/9 -40
			—	—
			Schizophrenia paranoides?	3/9 -40
			Schizophrenia? ?	3/12-40
2.6		500 g 20 %	—	
			Schizophrenia (Hebephrenia)	25/9 -40
			—	—
2.9		500 g 20 %	—	—
			Melancholia in Psykopathiam?	25/9 -40
			—	—
			—	—
			—	—
2.3		500 g 40 %	—	—
3.0		500 g 40 %	Melancholia hypochondrica	28/11-40
with 10 ml 40 % glucose injected intravenous 2.0				
			Schizophrenia (incipiens)	9/1 -41
with 7 ml 50 % glucose injected intravenous 2.8	1/4 h. after 500 gr 40 % saccharose solution per os. 2.9			
			Psykopathia	21/1 -41

It will be seen from tabel 1 that most of the values during precoma and coma lie below the lowest value for normal fasting subjects. In the cases in which the amino acid-N is determined before the insulin injections a great fall is observed during the treatment.

In the experiments in which the amino acid-N was determined after the awakening of the patients with saccharose given by stomach tube or by intravenous glucose injections a further fall in the amino acid-N in plasma is seen. The time elapsed between the blood samples in insulin coma (or precoma) and the awakening of the patient was about 15—25 min. when the patient was waked by stomach tube and 5 min. when the patient was waked by an intravenous injection. It will be seen that both methods for awakening cause the amino acid-N in plasma to fall to extreme low values. It seems thus that the amount of sugar given is insignificant. And from the experiment on M. C. it will be seen that saccharose given to the patient after the awakening by a glucose injection does not cause a further decrease of the amino acid-N in plasma.

To ascertain that the administration of sugar does not cause a lowering of the amino acid-N in subjects to whom no insulin is given the experiments shown in table II were performed.

Tabel II.

Influence of sugar and water given per os on the amino acid-N in plasma.

Subject	Sex	Date	The amino acid-N in plasma in mg %		
			fasting		
C. T.	♂	7/1-41	4.2	¼ h. after 500 g water per os 3.9	¼ h. after 100 g saccharose per os 4.3
—	—	11/1-41	5.0	¼ h. after 200 g saccharose dissolved in 600 g water (per os) 4.9	1 ½ h. later 4.8
K. G. N.	♂	18/1-41	3.9	¼ h. after 200 g saccharose dissolved in 550 g water (per os) 3.7	1 ¼ h. later 3.8

It will be seen that large amounts of saccharose and of water only cause slight variations in the amino acid-N in plasma. (The one of the subjects K. G. N. was here examined after the insulin treatment the other was a normal individual).

It is at present very difficult to understand that the awakening of a patient from insulin coma by administration of sugar cause a further fall in the amino acid-N in plasma, but the results may in the future be of some interest for the understanding of the way in which insulin exerts its influence on the nitrogen metabolism and for the understanding of the process of awakening.

### Summary.

The diminution of the amino acid-N in plasma after insulin injections as found by previous authors is confirmed.

It is further shown that the awakening of patients from insulin coma either by saccharose by stomach tube or by intravenous injections of glucose causes a further fall in amino acid-N in plasma. After the awakening further administration of sugar was without effect.

In subjects not in insulin treatment administration of sugar causes only slight changes in amino acid-N in plasma.

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Communication from Medical Ward B, Centralsygehuset, Slagelse, Denmark. Senior Physician: H. Aastrup, M. D.)

## The Duration of Life of the Erythrocytes in Hemolytic Jaundice Determined through Transfusion Experiments.

By

AAGE KIRKEGAARD and GERTRUD KIRKEGAARD.

(Submitted for publication October 27, 1944).

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During recent years it has been emphasized that the duration of life of the erythrocytes cannot always be interpreted in the same manner. According to Schiödt (14) two different theories must be considered, according to whether the vitality of the erythrocytes or the destructive powers of the surroundings have the decisive influence on the destruction of the blood corpuscles; we shall revert to these two theories, the longevity-theory and the destruction theory.

To determine the duration of life a series of different methods have been used, of which Schiödt, in 1938, gave a survey, to which we refer. Whilst these methods have given rather different results as far as normal erythrocytes are concerned, it is generally agreed that the duration of life of the spherocytes of hemolytic jaundice is considerably shorter than that of normal erythrocytes. This corresponds well to the intense regeneration phenomena found in this disorder.

The duration of life of the spherocytes seems to have been determined previously only by means of calculations on the basis of the

Table 1.

Previous determinations of the duration of life of the erythrocytes in hemolytic jaundice. The figures of normal erythrocytes found by the same authors are included in the Table.

Author	Hemolytic jaundice	normal	Method
Adler and Bressel ....	7—10 days	102—310 days	urobilin excretion <sup>1</sup>
Heilmeyer and Albus ..	2—8 "	(125) "	" " "
Lichtenstein and Terwen .....	10—13.6 " "	140 "	" " "
Morawitz .....	8—10 "	150—200 "	" " "
Dedichen .....	4—7 "		differential agglut.
Dekkers .....	23—76 "	51½—75½ "	" " "
Placeo .....	a few days	40 "	" " "

<sup>1</sup> The duration of life computed without regard to back-resorption of urobilin, for which reason the values possibly must be divided by 4 (see text, p. 30).

<sup>2</sup> The latter figure found in patient with secondary hemolytic jaundice after malaria.

urobilin excretion [Adler and Bressel (1), Heilmeyer and Albus (6), Lichtenstein and Terwen (10), Morawitz (11)], which, as is known, is a measure of the amount of hemoglobin decomposed, and by means of the differential agglutination method [Dedichen (2), Dekkers (3)], in which it is examined for how long transfused erythrocytes of another group can be demonstrated in the recipient by means of agglutination with corresponding serum. Neither of these methods is very correct [Görl (5), Schiödt (14)], but still they show the shortened duration of life of the spherocytes of the hemolytic jaundice, as will appear from Table 1.

### The Writers' Examinations.

To determine the duration of life of the erythrocytes we used transfusion from a healthy individual to a patient with acquired, hemolytic jaundice, whose erythrocyte figure and hemoglobin percentage were constant, and examined by daily counts when the values of the time before the transfusion were reached again.

As the patient's blood contained a very great number of reticulocytes it was possible by counting the latter to get a control of the duration of life. When normal blood is added the reticulocytes



are »diluted», their percentage decreases. Gradually as the blood corpuscles added are destroyed the reticulocyte percentage increases again, and the period passing till the percentage of the time before the transfusion is reached expresses the duration of life of the erythrocytes, provided the patient keeps his reticulocyte production and his »own» erythrocyte figure at a constant level.

In our experiments the detailed procedure was as follows:

The patient's erythrocyte figure, reticulocyte percentage, and hemoglobin percentage were determined every day. When the values had been at a constant level for 4 consecutive days, 500 ml blood were transfused from a healthy individual and the determinations were continued till the original values had been reached. To make sure that these values were still constant, the determinations were continued for another 4 days.

The erythrocytes were counted in the usual manner in Hayem's fluid in Bürker-Türk's counting chamber. The limits of error are computed as  $3 \sqrt{\text{number counted}}$ . The hemoglobin percentage was determined with a Zeiss hemometer and the reticulocytes were counted according to the method stated by Kaj Larsen and Skadhauge (9). All determinations were made on blood from the ear, taken at the same time every day and drawn into the pipette 3 minutes after pricking the ear [Gregers Sørensen (15)].

Carried out in this manner the method does not seem to have any certain fallacies other than those connected with the hemometry and the counts themselves, and for this reason we have always made the determinations in duplo or in triplo and counted 1500—3000 erythrocytes and 15—1600 reticulocytes in each determination, at the initial values 4 times and double the number respectively.

But there are a few hypothetical fallacies, because there is a possibility of damaging the erythrocytes in the course of the transfusion and of the latter having a stimulating effect on the bone marrow. These fallacies, however, are hardly of any great importance, especially not the latter, as the figures remained fairly constant in the after-period. In using the reticulocyte percentage instead of the absolute figures per  $\text{mm}^3$  the influence of possible fluctuations in the amount of the plasma has been avoided.

The results will appear from Fig. 1 showing that »status quo» was arrived at in 6 days, as far as the erythrocytes and the hemo-

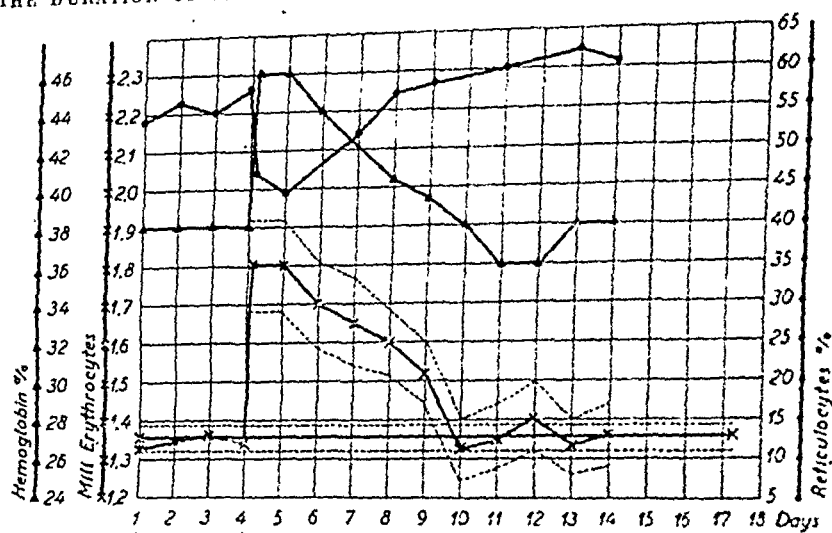


Fig. 1. Determination of Duration of Life of Normal Erythrocytes in Blood-stream of Patient with Hemolytic Jaundice.

×—×— Erythrocytes per mm<sup>3</sup> with limits of Error  $\pm 3 \sqrt{\text{number counted}}$ .

▲—▲— Hb %

●—●— Reticulocytes %

On the 4. day transfusion of 500 ml blood.

globin percentage are concerned, and 4--5 days in the case of the reticulocytes.

### Discussion.

What these results mean to the duration of life of the blood corpuscles depends on which of the theories referred to in the introduction we make the basis of our considerations. In the following we shall briefly recapitulate these two theories.

According to the longevity-theory the duration of life of the erythrocytes is a congenital property and quite independent of the destruction, which only works passively. Every day a certain number of erythrocytes have reached the end of their days, they die and are removed, but as the number of erythrocytes of the individual is a constant one under normal conditions, an equally great number of erythrocytes must be produced in return. If we state the duration of life of the erythrocytes to be  $n$  days, the amount of erythrocytes formed per day and the amount removed per day must be  $1/n$  of the total amount of erythrocytes. A curve of the age distribution among the erythrocytes contained in 1 mm<sup>3</sup> blood will then get a horizontal course with a sudden decline on the  $n$ th

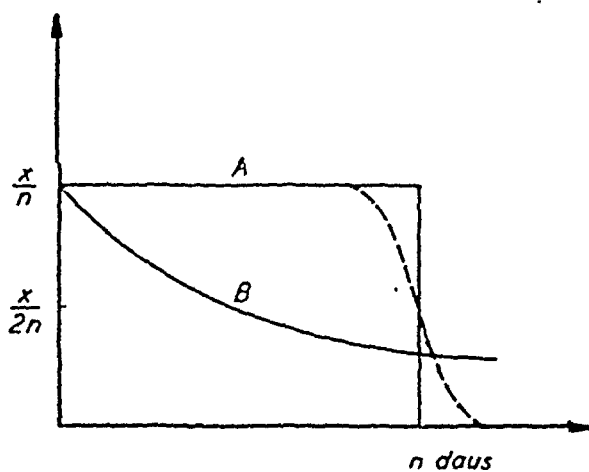


Fig. 2.

Age distribution of the erythrocytes in 1 mm<sup>3</sup> blood according to the longevity-theory (A) and the destruction theory (B). (according to Schlödt).  
Absciss: Age in days.

Ordinate: Number of erythrocytes in a unit which is  $x/n$ , where  $x$  is the number of erythrocytes per mm<sup>3</sup>.

day, or rather, as  $n$  must be supposed to be an average value, a decline as shown by the dotted line in Fig. 2. Provided that a blood transfusion does not bring about any alteration of the individual's own erythrocyte production the conditions must be as shown in Fig. 3 A after such a transfusion: Every day  $1/n$  of the transfused erythrocytes will perish, and therefore the erythrocyte figure will fall along a straight line to its former value, which is reached, after a period corresponding to the duration of life of the erythrocytes. It will easily be seen that after an acute loss of blood, provided it does not alter the individual's own erythrocyte production, the regeneration will also take place along a straight line and that the time of regeneration will just be the duration of life of the erythrocytes.

According to the destruction theory the breaking down of the erythrocytes is due to an active process, the extent of which depends on the number of erythrocytes but is quite independent of their age. On the first day a «litter» of erythrocytes lives, say  $1/n$  of them will perish, the next day  $1/n$  of the rest and so on. A curve showing the age distribution of the erythrocytes in 1 mm<sup>3</sup> blood will then be a logarithmic curve approaching 0 like an asymptote

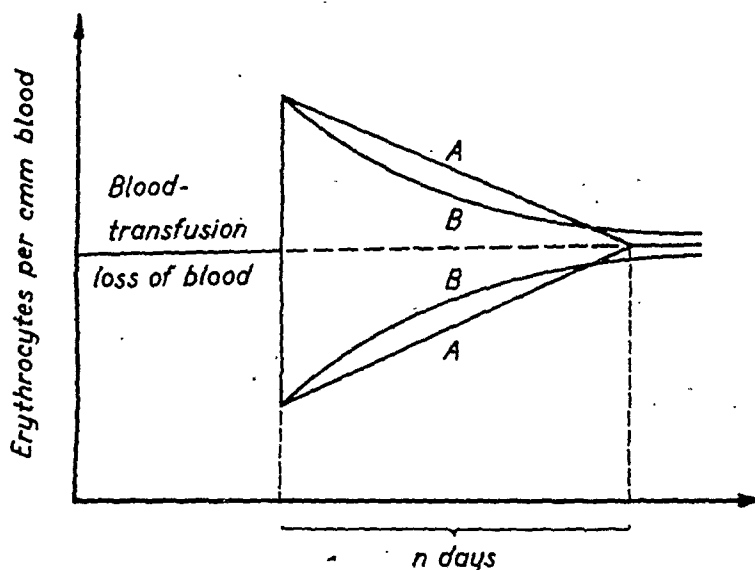


Fig. 3.

The decreasing and increasing number of erythrocytes after a blood transfusion or after an acute loss of blood, according to the longevity-theory (A) and the destruction theory (B).

according to the formula:  $a - x = a \cdot e^{-KT}$ , where  $a$  is the daily production,  $x$  the amount destroyed till the time  $T$ ,  $e$  the base of the natural logarithm and  $K$  a constant (Fig. 2 B).

Now suppose that in a transfusion the recipient keeps his own erythrocyte figure at a constant level; the decline of the total erythrocyte figure will then take place according to a curve parallel to the above. This curve will, like an asymptote, approach the erythrocyte figure of the time before the transfusion, i.e. the curve becomes bent, which corresponds to the decreasing destruction with decreasing amount of erythrocytes (Fig. 3 B).

On looking at the curve Fig. 2 B we must say that according to the destruction theory we cannot call the duration of life a property of the erythrocytes, as it is quite accidental when the destruction overtakes them. But on a purely mathematical basis we can find the average time of existence.

When judging our results it will be necessary to consider them on the basis of each theory. According to the longevity-theory the duration of life is simply the time passing till the recipient's erythrocyte figure is the same as before the transfusion. Presuming a certain variation of the duration of life the above will be the dura-

tion of life of the longest livers, whereas the average duration of life must be supposed to be a little shorter.

But it is impossible to compute the duration of life in our experiments according to the destruction theory, as the curve does not resemble any logarithmic curve at all.

The authors who have previously pursued the study of the duration of life of the erythrocytes in hemolytic jaundice all seem to have followed the longevity-theory; their results will appear from Table 1, but as the back-resorption of the urobilin, amounting to  $\frac{3}{4}$  [Eppinger and Charnas (4), Rous (13)], has not been considered we must doubtless reckon with durations of life of about  $\frac{1}{4}$  of those stated, i.e. 1—4 days, or a little shorter than those found by us. There seems to be a greater conformity between the 5—6 days found by us and Dedichen (2), who by means of the differential agglutination method finds that the transfused erythrocytes of another group can only be demonstrated in the recipient's blood 4—7 days after the transfusion.

It should, however, be borne in mind that we [like Dedichen (2)] used normal erythrocytes for the transfusion and that it is their duration of life in the diseased organism we determined, whilst the other investigators determined the duration of life of the patient's own erythrocytes.

Whilst in hemolytic jaundice the duration of life of the erythrocytes seems to be a few days only, possibly a week, the duration of life of normal erythrocytes is presumably 30—40 days [Kirkegaard and Kaj Larsen (7, 8), Schiödt (14) et al.]. Similar normal figures are also found in Table 1 when the back-resorption of urobilin is considered. It will thus be seen that in hemolytic jaundice the duration of life of the erythrocytes is about  $\frac{1}{10}$ — $\frac{1}{20}$  of the normal, whilst normal erythrocytes live for about  $\frac{1}{5}$ — $\frac{1}{10}$  of their lifetime if transfused to a patient with hemolytic jaundice.

These results are not without interest to our perception of the pathogenesis of the hemolytic jaundice. The point at issue has here been whether the hemolysis is due to primary alterations in the erythrocytes themselves or to a primarily increased destructive power of the spleen and the reticuloendothelial system. As even the normal erythrocytes according to the above are destroyed very rapidly in patients with hemolytic jaundice, these experiments support the latter theory. It was, therefore, to be expected that

we should find a curve in conformity with the destruction theory, a bent curve. As this was not the case the curve will support the longevity-theory. It must then be supposed, provided the curve is correct, that the active destruction befalls the oldest erythrocytes, or that the originally normal blood corpuscles are influenced in some way (hemolysin?), their duration of life thus being considerably shortened.

### Summary.

Despite their inaccuracy the methods previously employed in determination of duration of life of the erythrocytes in patients with hemolytic jaundice have shown the duration of life to be about  $1/10$ — $1/20$  of the duration of life of normal erythrocytes.

On transfusion of normal erythrocytes to a patient with primary, acquired hemolytic jaundice erythrocyte figure, reticulocyte figure, and hemoglobin percentage reached the original values 4—6 days after the transfusion.

The result is discussed with a view to the longevity-theory and the destruction theory, and it is seen that normal erythrocytes only live  $1/5$ — $1/10$  of their normal lifetime when transfused to a patient with hemolytic jaundice.

Consequently the rôle of the spleen in the pathogenesis of the hemolytic jaundice seems to be a dominant one, at any rate in the primarily acquired form.

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From the First Medical Clinic, Sahlgren's Hospital, Gothenburg (Sweden).  
(Acting Head: Dr. Bo Ewert, M. D.)

## Intermittent claudication and vascular spasm.

I. Is vascular spasm a contributory cause of intermittent claudication in patients with structural disease of the arteries?

By

TORSTEN LINDQVIST, M. D.

(Submitted for publication January 26, 1945).

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### Introduction. Brief criticism of the literature.

When Charcot (1), in 1858, published the first description of the complex of symptoms which is now generally called intermittent claudication he suggested that the symptoms might be due to the presence of far-reaching structural disease of the arteries. He used the terms »paralysie douloureuse ischaémique» and »claudication intermittente par oblitération artérielle». Both of these expressions are reflections of his opinion that the symptoms arise from the disturbance in the blood supply resulting from pathologically obstructed arteries. This was the view held by all investigators for the next forty years.

Erb (2) seems to have been the first to find this explanation inadequate. He believed that narrowing of the arteries due to structural changes was not always the only genetic factor but that vascular spasm must also contribute towards the end result in some cases. This theory has been favoured by many authors, among whom the following should be mentioned: Oppenheim (3, 4), Curschmann (5, 6, 7), Westphal (8), Cassirer (9), Cassirer and Hirschfeldt (10, 11), Osler (12), Müller (13), André-Thomas and Valensi

(14), Sunder-Plassmann (15). While some authors felt uncertain as to whether vascular spasm occurs in every instance or whether it is merely an auxiliary cause in certain cases, others were firmly convinced that it always occurs in connection with intermittent claudication, and that it plays a decisive part in producing the syndrome. This last-mentioned theory is advanced, for instance, in the well-known textbooks by Strümpell-Seyfarth (16) and by von Bergmann (17).

Lewis (18), on the other hand, refused to admit the idea that arterial spasm contributes towards producing the symptoms in intermittent claudication. »The reason is in all instances to be found in relative ischaemia of a working muscle» (p. 39). — »Much has been written of pathological states in which both structural disease and increased vasomotor nervous tone are considered each to contribute to the end result. I have been unable to find any satisfactory evidence that such states occur» (p. 59).

Lewis by no means denies the fact that a person with structural vascular disease who is exposed to vasoconstrictive stimuli reacts to the stimulation with a vascular contraction apparently more powerful than that occurring in a subject with normal blood vessels. On the contrary, he places much emphasis on the fact that »Raynaud's phenomenon» is more likely to be observed in persons with this type of vascular disease, after exposure to cold for instance, than in normal individuals. He points out, however, that this should not be interpreted as »Raynaud's disease»; in other words, as an increased tendency to vascular spasm. It is to be explained simply by the fact that an essentially normal vascular contraction has a more easily distinguishable effect in the ill, in whom the blood flow is already impaired, than in those with normal vessels. This view, which in all probability is the correct interpretation, was not taken into consideration by many of the abovementioned authors. These investigators have often asserted instead that it must be a question of vascular spasm when the foot becomes paler in a person with intermittent claudication than it does in a person with normal circulation on exposure to cold. Thus, this »proof» of the existence of vascular spasm does not seem to be sound.

In support of their theory with regard to vascular spasm these authors also mentioned the following facts. In patients with intermittent claudication the foot becomes cold after exercise, and turns



same pressure, during the 45 seconds immediately following the work of sitting up and lying down twenty times, while in figure 2 C we see the tracings obtained during the succeeding 45 seconds. It will be observed that after this comparatively moderate activity there was a decided decrease in the pulsations in the calf, but that while the patient was resting the pulsations gradually increased until, 3 minutes after the cessation of the work they had returned to their original size.

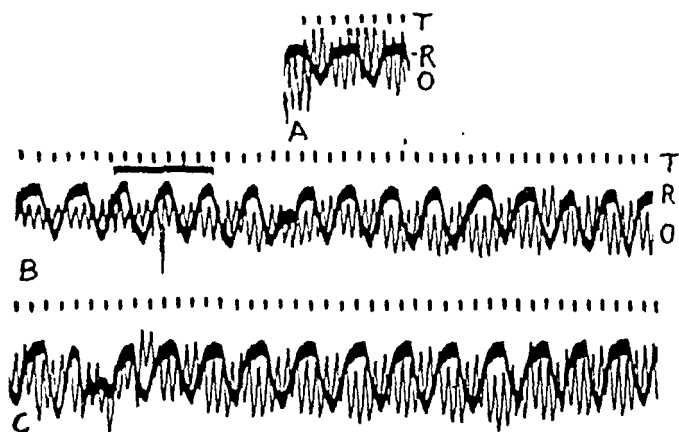


Fig. 2. Case 1. A, shows oscillations with pressure of 60 mm in the resting limb; B, oscillations with pressure of 60 mm 1—45 sec. after exercise; C, oscillations with pressure of 60 mm 46—90 sec. after exercise. T = time in seconds, O = oscillations, R = respiration.

In general, the decrease in the pulsations after exercise was more noticeable on the left side than on the right. When the subject was resting the pulsations were of about the same size on both sides. Thus, the arterial spasm after exercise was more marked on the side on which the sympathectomy had been perfect than on the side where there was still a certain amount of activity in the sympathetic nervous system.

Unfortunately, as Dr. Lax had to return to Hungary on account of the approaching war, we had to abandon our plans to follow up our investigations in this case by testing the effect produced by certain drugs on the arterial spasm, as well as to extend our studies to other patients with similar symptoms. It has not been possible to resume our work together.

*Case 2. G. H., aged 61. A photo engraver. Record. No. 160/44. At the beginning of 1941 his foot began to cause trouble by growing numb when he walked. In January 1942 he began to experience severe pains in the left calf on walking; these pains receded a few minutes after he stood still. When he was examined in January 1942 the oscillations in the left and right thighs and the right calf were normal, but in the left calf they were greatly decreased. The measurements of the pulsations in the calf were always taken on the thickest part of the calf. For this examination as*

well as for all the other oscillometric measurements described in the remainder of this paper a Recklinghausen oscillometer with an alternating scale was used. He was treated with priscol and a considerable improvement was noted. As the pains became worse again at the beginning of 1943 a lumbar sympathectomy on the left side was done in March 1943 (Dr S. Lembke). After this intervention the discomfort in the left leg was very slight. At the end of 1943, however, he began to have pain of a similar nature in the right leg. Oscillometric examination in January 1944 proved that the pulsations in the right calf, which had been 40 mm at the most two years previously, had now dropped to 6 mm. Measurement of the skin temperature in the toes, with a rising body temperature, by a technique described by the author [Lindqvist, (26)], indicated arterial obstruction of some severity in the right leg. Arteriographic examination with perabrodil disclosed that the upper part of the femoral artery in the right leg was abnormally narrowed. Ten centimetres above the knee joint the artery was completely occluded for a length of 5 cm. In this area there were numerous collateral anastomotic channels. The popliteal artery and the arteries of the lower leg were strikingly narrow. As the administration of priscol brought no improvement, a lumbar sympathectomy on the right side also was performed towards the end of January 1944 (Dr. S. Lembke). He was a little better after the operation, but the signs and symptoms of intermittent claudication began to increase in severity again and soon, even after a walk of 50 metres, there were severe pains in the right calf.

At an oscillometric examination on May 17, 1944, the pulsations in the right calf were now no higher than 3 mm. After the patient had walked 30 metres the pulsations immediately after this exercise were hardly visible, being  $> \frac{1}{2}$  mm. After 2 minutes' rest they had increased to 1.5—2 mm and after 4 minutes' rest they had reached the same size as before the exercise. No pains had appeared after the walk.

As I had obtained with estrone injections an effect which seemed favourable in other patients with vascular occlusion, and as other authors [e. g. Ratschow, (22)] also recommend this treatment, a course of injections of Ovex Leo, 10,000 international units, was instituted. They were given daily to begin with, the interval between each injection being gradually lengthened until finally one week was allowed to elapse between each. Under this treatment he reported himself that there was an improvement.

At another oscillometric examination on Aug. 25, 1944 the oscillations on the right calf had increased to a maximum value of 5 mm. There was no definite change in the size of the oscillations after the patient had walked 30 metres. After a 200 metre walk, in connection with which the patient had severe pain in the right calf, the oscillations rose to a maximum of 7 mm.

*Case 3.* O. A., aged 58. A sea captain. Record No. 2109/44. For a couple of years he had mild pains in both calves, severest on the right side. The pains appeared while he was walking and receded rapidly when he rested. During the past few months the condition in the right calf had become intensified, a walk of even 100 metres causing severe pain.

When he was examined in September 1944 the pulse was readily palpated in the groins but pulsations were not distinguishable in any other part of the legs. Radiographic examination of the legs revealed the presence of advanced calcification of the walls of the arteries of both the thighs and the lower legs. Measurement of the skin temperature in the toes with a rising body temperature, by my own method, indicated that there must be serious arterial obstruction on both sides.

The largest oscillations in the left calf were 12 mm. After the patient had been in a state of complete rest for several hours the oscillations in the right calf reached a maximum of 5 mm. After he had walked 200 metres, as a result of which he had severe pains in the right calf, the oscillations in the right calf were hardly visible and too small to be recorded. While he was resting they began slowly to increase again but even at the end of half an hour they had not returned to their normal size, remaining instead at 2.5—3 mm.

*Case 4.* A. L., aged 65. A laboratory assistant. Record No. 2746/43. In September 1943 his left foot began to ache and to feel stiff and cold. When he walked his left calf became stiff and painful. This discomfort receded rapidly when he rested. At the beginning of December 1943 the pains in the left foot became much worse, he had almost unbearable pain even when he was resting and it was due to the latter condition that he was hospitalized on Dec. 6, 1943. His left foot was then very cold. The pulse was palpable in the groins and in the middle of the thigh on both sides. In the popliteal fossa, the pulse was palpated on the right side but not on the left. The posterior tibial artery was not palpable on either side. The dorsalis pedis artery was pulsating faintly on the right side but was indistinguishable on the left side. As the pains continued to increase in severity despite the fact that he was lying in bed incipient gangrene was suspected, and he was transferred after a few days to surgical ward I. After a short time, however, the pains receded. It was found by oscillometric examination that the pulsations were almost entirely suspended in the left calf, being  $< 1$  mm, while in the right calf they reached a maximum of 13 mm. In the middle of the left thigh they went as high as 13 mm and in the corresponding area in the right thigh they were 19 mm. Radiographic examination of the left leg without the use of a contrast medium revealed a moderate degree of calcification between the first and second metatarsal bones but there was nothing else of interest. An arteriographic examination with per brodil was carried out on Jan. 10, 1944. The femoral artery, from its entry into the adductor canal and downwards, was seen to be arteriosclerotic, with irregular margins and a distinctly narrowed lumen. The contrast medium was flowing to the lower leg partly through large collaterals, but partly also through the narrowed main artery. Severe arterial obstruction was established by measurement of the skin temperature in the toes with a rising body temperature.

On Jan. 26, 1944 three sympathetic ganglia in the lumbar region on the left side together with the intervening parts of the sympathetic chain

were removed (Dr. S. Lembke) The foot became warmer after this, and the spontaneous ache disappeared. After a time, however, the pains in the left calf re-appeared when he walked but they receded at once when he rested.

At an oscillometric examination of the left calf on July 28, 1944 the pulsations were found to be much larger than they had been before the operation, the maximum value being 4 mm. After he had been walking for 6 minutes he had distinct pains in the left calf. He was again examined by oscillometry, and it was now found that the oscillations were much larger than before the exercise. These features are illustrated in figure 3. The oscillations had already returned to their previous size three minutes after the termination of the exercise.

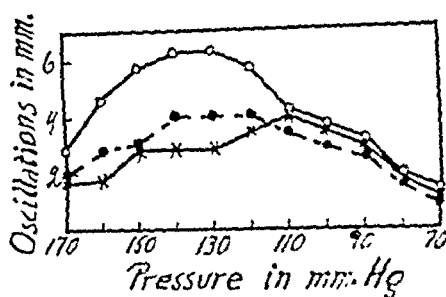


Fig. 3. Case 1.

- x—x— Oscillations before exercise.
- o—o— Oscillations immediately after exercise.
- Oscillations 3 minutes after exercise.

Case 5. I. J., aged 58. A carpenter. Record No. 797/44. He had been suffering for several years from a complaint diagnosed as vitium cordis, on account of which he had spent some time in hospital in 1942. Both the aortic and the mitral valve were impaired. For the past five years he had been suffering from pains in both calves, severest on the left side, after he had walked about 200 metres. If he continued walking the pains became so acute that he was forced to stop and rest. They then receded rapidly.

In March 1944 the pulse was felt to be normal in the groins but no pulse could be palpated in the popliteal artery or the arteries lower down on either side. By measuring the skin temperature in the toes with a rising body temperature it was found that the left leg was affected by severe arterial obstruction; the circulation on the right side was slightly better, but it was not normal.

The results obtained from the oscillometric examination of the left calf, both when the patient was resting and after exercise, are shown in figure 4. After the patient had been walking for 5 minutes, during which time pains were distinctly felt in the left calf, the oscillations in this region became almost twice as large. After another 5 minutes' walking the tracings were exactly the same as after the first five minutes. The examination was carried out on July 28. A later examination yielded the same result.

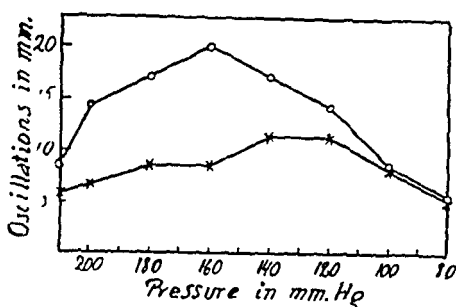


Fig. 4. Case 5.

—x—x—x— Oscillations before exercise.  
 —o—o—o— Oscillations after 5 minutes' walk.

*Case 6.* N. L., aged 58. A merchant. Private patient, no. 768/44. At the end of May 1944 he began to have pains in the right calf on walking. These receded almost at once when he rested. His right foot also became slightly cold.

At an examination in the middle of June 1944 all the pulses in the left leg were normally palpable, but in the right leg the pulse could not be distinguished in the popliteal fossa or lower down the artery. Oscillometric examination yielded normal pulsations in the left calf (30 mm) but the pulsations on the right side were greatly reduced. After a course of estrone injections in July 1944 he was improved but not wholly free from pain.

When examined on Sept. 1, 1944 he had pulsations of 5 mm in the right calf while resting. After walking for 20 minutes he experienced intense pain in the right calf. The oscillations now rose to a maximum of 7—8 mm; in other words, a very slight rise. After 5 minutes' rest the pulsations had resumed their original size.

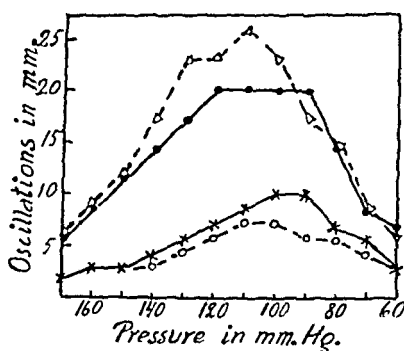


Fig. 5. Case 7.

—x—x—x— Oscillations of right calf in resting limb.  
 —o—o—o— Oscillations of right calf after 20 minutes' walk.  
 —•—•—•— Oscillations of left calf in resting limb.  
 —△—△—△— Oscillations of left calf after 20 minutes' walk.

*Case 7.* S. K., aged 44. A doctor. Private patient, no. 750/44. In April 1944 he had begun to suffer discomfort from pains and numbness in the right foot on walking, and soon after this he began to have pains also in the right calf when he walked. These pains receded almost at once when he rested.

When he was examined on June 14, 1944, it was discovered by means of skin temperature measurements in the toes, with a rising body temperature, that there were signs of a fairly massive occluding process in the right leg. The left leg appeared to be normal.

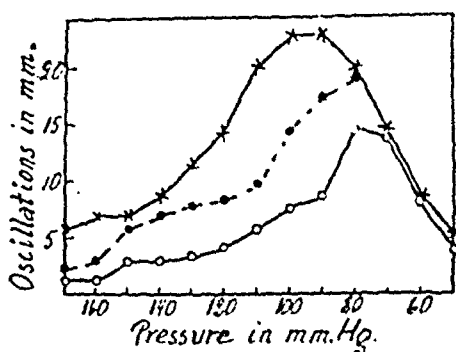


Fig. 6. Case 8.

- x—x—x— Oscillations of left calf in resting limb.
- o-o-o-o- Oscillations of left calf immediately after 45 minutes' walk.
- .....+..... Oscillations of left calf 3 min. after 45 minutes' walk.

The oscillometric recordings obtained before and after exercise are shown in figure 5. It will be seen that the oscillations in the left calf are within the normal range [cf. Ratschow, (22); Philippides, (27)]. After a 20 minutes' walk the pulsations had become slightly larger in the left leg. In the right leg, on the other hand, where the oscillations had been considerably smaller before the muscle work, they became still smaller after the walk, although the reduction was not especially pronounced.

*Case 8.* K. E., aged 45 years. A merchant. Private patient, no. 1140/44. For the past 3—4 months he had been experiencing pains in the left thigh and calf when he went for long walks. The pains appeared first in the calf, and if he continued walking they went up into the thigh, reaching as far up as the groin. After about 5 minutes' rest the pains disappeared. He was investigated by me in the beginning of October 1944.

The pulse was palpated in all the usual places in the right leg. In the left leg, the pulse was felt in the inguinal region. It was also palpable in the popliteal fossa but here it was weaker than on the right side. In the foot the pulse was not clearly distinguishable.

Determination of the skin temperature in the toes with a rising body temperature indicated the presence of a mild degree of arterial occlusion in the left leg.

Oscillometric examination proved that in the resting limb the pulsations in the left calf went as high as 22 mm and thus were within the normal range, but in the right calf they were 40 mm and thus the pulsations in the left leg could not be described as normal. Figure 6 shows the tracings obtained after rest and after exercise. We see from this figure that in consequence of a walk lasting 45 minutes, after which time there were only mild pains in the left leg, there was a marked decrease in the pulsations in the left calf. After 3 minutes' rest the pulsations showed a considerable increase. At the end of 9 minutes they had resumed their original size.

*Discussion.* It is clear from these case reports that in some cases of intermittent claudication a considerable decrease in the oscillations in the affected calf occurs in connection with exertion (cases 1, 2, 3, 7, 8). A decrease of this kind is to be observed not only in cases where the sympathetic innervation to the area in question appears to be completely cut off (cases 1 and 2), but also in those in which the sympathetic nerves have been left intact (cases 3, 7, 8). A decrease can be seen in cases displaying a high degree of arterial obstruction (case 1) as well as in those in which the occluding process has reached only moderate proportions (cases 7 and 8).

Obviously, however, it is not all cases of intermittent claudication that display this decrease in the pulsations in the painful calf after exercise. On the contrary, there is often an increase in the size of the pulsations in the working limb (cases 4, 5, 6). An increase of this kind occurs both in patients upon whom an apparently successful lumbar sympathectomy has been performed (case 4) and in those in whom the innervation by the sympathetic fibres is unimpaired (cases 5 and 6).

Especial interest is attached to case 2, where there was a marked decrease in the pulsations after exercise at first but where, after a long course of estrone injections, there occurred a distinct increase in the oscillations in connection with work. Observations from several similar cases are necessary before it is possible to decide whether this finding can be considered to have a general application.

Is this frequently occurring decrease in the pulsations to be interpreted, then, as an abnormal arterial spasm, or can it be regarded as a normal reaction in a segment of an artery containing pathologic changes in accordance with the line of reasoning suggested earlier in this paper with regard to the arteries in the skin on the foot?

In order to find an answer to this question it is necessary first of all to know how the oscillations in the calf behave in the working limb. This aspect has been studied fairly thoroughly by André-Thomas (28), who found there was an increase in the pulsations. These findings were verified later by Ejrup (25). I myself have examined about 20 healthy subjects from this point of view, and my experience has been that there is always a noticeable increase in the size of the oscillations in connection with exercise. Some of these examinations were carried out as early as 1939, while I was working in collaboration with Dr. Lax at the National Hospital in London.

Thus, when the normal reaction of the arteries in the calf to exercise is a dilatation which makes itself apparent in an increase in the size of the pulsations, it would seem logical to assume that a decrease in the pulsations is a sign of a pathological spasm of the arteries.

Hustin (24), however, strongly opposes this view. In his opinion, the decreased pulsations are not signs of an active vascular contraction; they are wholly and solely the result of an impairment of the blood flow. The muscles situated above the obstruction require an increased amount of blood during exercise, and there will then be a purely passive decrease in the supply to the segment of the vessel below the obstructed area; the pulsations in this area thus automatically decrease.

One objection that can be made to this reasoning is that in normal subjects the blood supply to the working limb is sufficiently abundant to furnish not only the muscles in the upper part of the leg but also those lower down with the larger amount of blood that is required. If the muscles of the thigh in normal persons do not »steal» the blood from the muscles lower down during exercise, why should this occur in persons with vascular disease in whom the blood flow to the lower part of the leg is in any case smaller than it is under normal conditions?

In support of his theory, Hustin stresses the fact that when the skin temperature in the toes is being measured after spinal anesthesia, in patients with arterial obstruction, there is sometimes a drop in the temperature instead of the usual elevation. The blood is conveyed to other areas, the feet receive less than before. His observation is undoubtedly correct. I myself have had the oppor-



tunity to observe several cases in which there was a drop in the temperature in the toes after spinal anesthesia. My attention was first drawn to these cases by Dr. T. Sahlström. The interpretation we always placed on this phenomenon, however, was that it was due to the lowering of the blood pressure occurring in connection with spinal anesthesia; this drop causes a reduction in the blood flow. But there is no lowering of the blood pressure during exercise; on the contrary, it rises, and the conditions in the working limb are therefore not analogous to those following spinal anesthesia. Thus, the conclusions reached regarding one type of experiment can not be applied to the other type. It seems to me, therefore, that the decreased pulsations are not to be explained as a physiological reaction in a vascular system in which there are structural abnormalities. The only other solution would seem to be to interpret them as pathological contractions of the arteries; in other words, as arterial spasm.

The question of whether arterial spasm has any share in producing intermittent claudication might therefore be answered by saying that in certain cases of structural vascular disease arterial spasm occurs in connection with exercise, causes a further reduction in the blood supply to the working muscle, and thereby helps to aggravate the symptoms. Spasms of this type do not occur in all patients, however, and in those in whom they do not occur the structural narrowing of the vessel and the consequent relative degree of ischaemia must be regarded as the only explanation of the symptoms.

Nothing can be said with certainty as yet with regard to the reason why these spasms occur in certain patients. As the present investigation has shown, it is beyond all doubt that they can occur in cases where no sympathetic impulses are reaching the vessels of the calf from higher centres, and the cause in these cases can thus under no circumstances be an increase in the vasoconstrictive impulses passing through the sympathetic nerves. There is no reason, therefore, why this factor should be of any particular significance in cases where the sympathetic innervation is unimpaired. This point needs to be stressed because it is often asserted in the literature that all arterial spasms are to be regarded as being due to an increase in activity by way of the sympathetic innervation [cf. Sunder-Plassmann, (15)]. The question of whether the sym-

pathetic nervous system plays any part in the production of arterial spasm in a given case can be decided by studying the oscillations before and after work, under ordinary conditions and after complete blocking of the lumbar sympathetic system has been achieved. [For further details, see Lindqvist, (29)]. That substances formed locally should be responsible for the spasm is now no longer considered likely, the present conception being instead that substances possessing marked vasodilatory properties are formed in an ischaemic area. [For summarized accounts of the mechanism see Lewis, (18), and Ratschow, (22). See also Lewis, Pickering and Rothschild, (30)]. Further investigations on the influence exerted by various pharmaceuticals in the occurrence of the spasm may possibly provide information both as to the cause of the spasm and to a suitable therapy.

Thus, a complete investigation on a case of dysbasia intermittens ought to throw light on whether the signs and symptoms are due solely to structural contraction of the arteries or whether arterial spasm is also present. Only by means of oscillometric examinations carried out both on the resting and the working limb can we obtain an answer to this question.

### Summary.

There is still much uncertainty as to whether arterial spasm contributes towards producing the syndrome in intermittent claudication. After a critical study of the reasons advanced in the literature to account for the existence of arterial spasm the author comes to the conclusion that it is quite possible that arterial spasm can be present in intermittent claudication but that there is no proof that such is the case.

In his own series of intermittent claudication cases the author finds that a decrease in the oscillations in the calf can occur in the working limb but that in some cases there is instead an increase in the size of the oscillometric tracings. A decrease in the tracings is found in both severe and mild forms of vascular disease, and both in patients with unimpaired sympathetic innervation and in those who have undergone a successful lumbar sympathectomy. In the cases where there is a decrease in the pulsations the only explanation seems to be a pathological arterial spasm.

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From the Medical Clinic (Director: Professor Sven Ingvar) of the Royal University at Lund (Sweden).

## Contribution to the knowledge of the pathogenesis of amyotrophic lateral sclerosis.

By

ERIK ASK-UPMARK, M. D.

(Submitted for publication January 16, 1945).

Amyotrophic lateral sclerosis is, although a rather rare disease, of particular interest with regard to the nosography, since it represents a syndrom involving the upper as well as the lower motor neuron. The symptomatology is hence extremely characteristic; the connection of atrophy of the muscles of the hand, particularly so the thenar and hypothenar eminences, with pyramidal symptoms, not least so with regard to the reflexes of the arm, and the absence of any sensory disturbances, is resembled by no other organic disorder of the nervous system. The disease thus represents a well-defined entity with regard to the clinical diagnosis, corresponding to a most typical pathological anatomy, affecting the motor cortex, the pyramidal tracts, the bulbar nuclei and the anterior horn cells. Whilst our knowledge about the clinical pathology hence is fairly complete, the problems about etiology and pathogenesis have remained almost as obscure as the therapeutical achievements have been poor. Briefly summarized, the following factors have been accused as causative agents.

1. »Exposure to cold, privation, fright, injuries such as fall on the back, virus and bacterial infections and toxic processes including lead poisoning — — — syphilis, chronic encephalitis — — »

(Davison in his chapter on amyotrophic lateral sclerosis in *Tices Medicine*).

2. An abiotrophy of the motor system, which is considered to have certain potentialities but when, towards the middle age, the strain on the system becomes too great degeneration is liable to start (Spiller and others).

3. An avitaminosis, represented possibly by the deficiency of vitamin E. This theory is based mainly on certain experiments in animals, which have been deprived of vitamin E and eventually developed a motor syndrom, somewhat resembling the disorder in question (Einarson et al.).

The present paper will attempt to furnish a contribution to our knowledge about these questions. It is based upon three cases, in whom amyotrophic lateral sclerosis has developed as a complication to other disorders of the nervous system. The observations run briefly as follows.

### Material.

*Case 1. Woman, aged 63, unmarried. Applied to my office Dec. 12th 1942. Invalidity since the age of 11, when she had poliomyelitis, with paresis of both legs. With the assistance of orthopedic boots and one stick she has been able to carry on to some degree indoors, busying herself with nursery and educational work but also with knitting and such works, her arms and hands being unaffected by the poliomyelitis. When outdoors she has been driving a tricycle by means of her arms. Last 5 years her hands, most so the right one, have been impaired, she has been unable to do small movements such as pulling a watch, knitting, writing. These symptoms have been particularly pronounced during the last year. — General condition good. Blood pressure 160/100. Both legs severely paretic, atrophied, cyanotic. Babinski negative. The thenar and to some degree the hypothenar eminences of the hands, most so the right, are atrophied, whilst the sensibility is entirely unimpaired and the reflexes of the arm are markedly increased.*

There could be no reasonable doubt with regaro to the diagnosis: amyotrophic lateral sclerosis in a woman, previously disabled by poliomyelitis of her legs. Subsequent examinations on repeated occasions have confirmed this impression.

*Case 2. Woman, aged 45, unmarried. (Med. Clin. 2104 and 2243/1939; admitted Aug. 24th, died Oct. 19th 1939). When 18 years of age poliomyelitis, causing remaining paralysis of both legs and paresis of lower half of the*

trunc but leaving the arms unaffected. By means of crutches and orthopedic bandages she has been able to carry on and was during the last 18 years teacher in a department for disabled. Nov. 8th 1937, i. e. not quite two years ago, she had an accident when one of the crutches gave away: she fell towards the wall with the right side of her head whilst the right shoulder was forced downwards, and the head thus bent over to the left side. She felt pains in the left half of her neck and her left shoulder but it was not until about 3 weeks later that a certain weakness of the left shoulder and the left arm did appear, connected with severe tremor. The pains and the tremor disappeared but the paresis of the arm eventually progressed so that in Sept. 1938 she was unable to use this arm. Examinations in other hospitals revealed a certain atrophy of the left arm and considerably increased reflexes of both arms, even clonus was obtained and Trömner was positive. Jan. 1939: the right arm began to be paretic, at first in the shoulder, later on also in its distal parts. During this year (1939) the speech has been impaired and slurred and at times dysphagia has been present as well. — The examination in the hospital on admittance did reveal a fair general condition, a moderately increased blood pressure (190/110), normal blood morphology and temperature, tachycardia. Neurologically she had without doubt a poor facial motility (masque), a complete, flaccid paralysis of both legs and abdominal wall, paralysis of the left arm and hand and paresis of the right shoulder and arm; the reflexes of the arms were extremely spastic, even so as to produce clonus. Her speech was difficult and slurred. Whilst in the clinic her general condition went downhill, urinary infection appeared, drowsiness became pronounced, the difficulties to speak and to swallow increased and she died Oct. 19th.

In this case the diagnosis was difficult. It was perfectly obvious that she had an old poliomyelitis, it was probable that she had achieved a certain Parkinsonism but the increased reflexes and the obvious pareses of the arms called for additional explanation. On account of the accident she had remained, during lifetime, a problem to the Accident Board. No injuries to the bones in her neck were brought about and as for a plexus injury this possibility was ruled out already by the fact that the paresis did not appear until 3 weeks after the accident, let alone that it was of spastic character. The possibility of amyotrophic lateral sclerosis was considered since the sensibility was entirely unaffected but the obvious Parkinsonism made it a bit uneasy to add a third disorder of the nervous system. The necropsy, however, which was performed by professor E. Sjövall, revealed besides of the old poliomyelitis not only a chroniciting process in corpus striatum and the unpigmented part of substantia nigra but also a most typical amyotrophic lateral sclerosis (fig. 1).



Fig. 1 a. Transection of spinal cord in case 2, stained ad modum Spielmeier. The involvement of the pyramidal tracts is easily to be recognized.

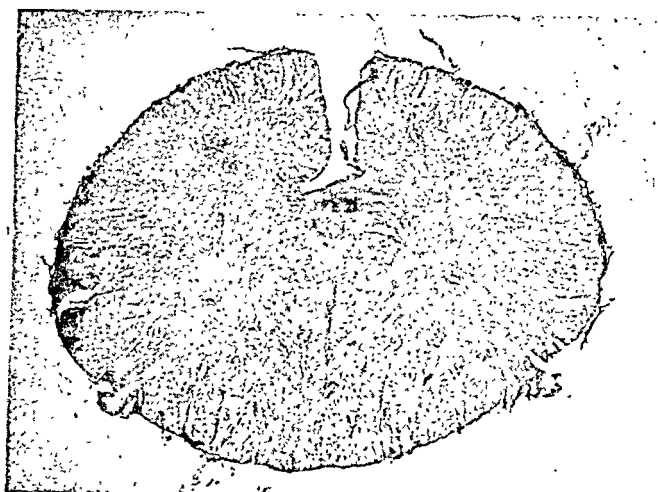


fig. 1. b. Transection of spinal cord in case 2, stained ad modum Mallory. The sclerosis of the anterior horns by means of gliosis is to be seen.

*Case 3. Man, aged 39 (Med. Clin. 3027/1944; previously examined in the clinic 1936, 1939 and 1940). Congenital spina bifida of L 3, L 4, L 5 and sacrum + Meningocele in the lumbar region + Hypertrichosis of the same region. Previously essentially in good health. 1933, i. e. 11 years ago dyspeptic disturbances, causing him to use diet; radiography of the stomach and the duodenum failed to disclose anything abnormal. During the last 10 years increasing weakness and rigidity of the legs, most so the*



Fig. 2. The hands of case 3. The marked atrophy of the muscles of the right hand is to be recognized. No disturbances of the sensibility. Pronounced spastic reflexes.

right one. Observed on several occasions in the clinic, presenting rigidity and spasticity of the legs (particularly the right), positive Babinski and positive Oppenheim. The meningocele was operated in 1936 with no improvement with regard to the legs. Various orthopedic interventions have been performed (tenotomy in the inguinal regions in 1942, orthopedic boots in 1943). During the last 5 years the symptoms have made it impossible for him to walk except by the help of a stick; he had also to give up carpentering, gardening etc. by means of which he had busied himself since the onset of the symptoms, previously doing engineering and driving. About 5 years ago a weakness was felt in the right hand and this weakness has continuously increased so that he, by now, is unable to use the hand for writing, dressing, eating and so on; the paresis has engaged also the right arm so that he has difficulties to put the right hand to the mouth. His general condition was at first fairly good but eventually the nutrition has suffered; his appetite has been very poor, disappearing already when he saw the food, he has had certain abdominal discomfort (dyspeptic disturbances from fat food) and his ability of eating has been impaired also by the condition of his right hand and arm and by his very poor dental state. His bowels have become sluggish and for the last 5 years he has had a feeling of anesthesia in the rectum, so that he is unable to feel when the defecation has been completely performed. The left eye has had a cataract for at least 9 years, more so during recent years. — The examination in the clinic revealed a somewhat reduced nutrition, a normal blood pressure and normal conditions from lungs, heart and abdomen, as observed by the physical examination. Dental condition poor. Mental abilities normal, although he for obvious reasons is somewhat depressed. He is able to walk by means of a stick but the gait is very much impaired, the right leg being almost completely paralytic. Babinski was positive, ankle jerks not to be eli-



cited. The left arm and hand does not present any paresis but he is unable to put his right hand in the neck. The right hand presents a most pronounced muscular atrophy and he is unable to extend the fingers; as a matter of fact it is a typical claw hand (*main en griffe*). The reflexes of both arms are considerably increased, Hoffman positive in both hands. The sensibility is entirely unimpaired. On previous occasions Wassermann has been examined repeatedly in blood and liquor and always been found negative. Myelography by means of air was performed some year ago and failed to disclose any expansive lesion whatsoever in the spinal canal, which was on the contrary rather wide in its distal parts, owing probably to the vertebral malformations present.

In this case the character of the lesion of the legs is difficult to ascertain but it seems probable that it is connected with the malformational conditions, demonstrated by the presence of a spina bifida + meningocele. The fact that the symptoms did not appear until the age of 29 does by no means rule out this possibility. With regard to the lesion of the arms, the connection of pronounced atrophy of the muscles of the hand with the intensely increased reflexes of the arms, the positive Hoffman and the unimpaired sensibility makes it probable that it deals with amyotrophic lateral sclerosis. It should be observed that the disorder of the legs did precede that of the hand by 5 years.

### Comment and discussion.

Among the three cases here described the diagnosis seems to be established with reasonable certainty by clinical means in the first and the last case, in the second case, which was perhaps the most complicated one, the diagnosis was suspected *in vivo* and eventually confirmed by the necropsy. All three cases have in common the development of amyotrophic lateral sclerosis in individuals previously disabled by other diseases with regard to the motility of their legs, in case (1) and (2) by poliomyelitis, in case (3) by a malformational condition of the spinal cord.<sup>1</sup> In all three

<sup>1</sup> A fourth similar case may or may not be represented by an old woman in the seventies who applied for assistance at my office because of a very severe arthrosis deformans of the hip joints, which had forced her to use crutches for several years. The muscles of her hands were without doubt atrophied as in amyotrophic lateral sclerosis, a corresponding weakness of the hands was experienced as well and no sensory disturbances suggesting any neuritis or syringomyelia were to be elicited. The reflexes of the arms were obviously vivid but if they were increased I could not tell with certainty, because of which this case has been excluded from the material, although it was felt to represent an amyotrophic lateral sclerosis as well.

instances the patients had to rely upon their arms and hands not only for the daily work but more or less also for the locomotion. It seems entirely possible that the heavy strain hence exerted upon the system of available motor neurons is liable to favour the appearance of the disorder in question. If such be the case one has obviously to reckon with the possibility of the development of amyotrophic lateral sclerosis in individuals accordingly disabled. The objections may be raised on the one side that not all individuals with more or less immobilized legs do present the syndrome here discussed, on the other hand that several instances of amyotrophic lateral sclerosis are liable to appear unheralded by another disorder of the legs. It is however obvious that the factor here stressed as responsible — the undue surmenage or exertion of the motor system in order to compensate the immobility otherwise experienced — should only be looked upon as a contributory cause. The aspect here marshalled is, however, entirely compatible with the idea of an abiotrophy of the motor system: in individuals accordingly disposed this abiotrophy is liable to be facilitated by the strain on the motor neurons still available for use. It is by no means impossible to harmonize this apprehension with the observations suggesting a deficiency disease due to the lack of necessary substances such as perhaps vitamin E. It is perfectly obvious that the nervous system and not least so the motor neurons are apt to suffer from a malnutrition and it may be remembered that in an otherwise entirely different condition, polioencephalitis hemorrhagica superior Wernicke, conclusive evidence has been brought forward, suggesting the character of a deficiency syndrome (cf. Neubürger's observations in man, Putnam-Alexander's in pigeons); the same goes, of course, for the affection of the spinal cord in pernicious anemia. With regard to the nutrition in the present material it may be said that case (2) and case (3) represented poor people, where the nutrition with certainty was not too good and whilst case (1) was fairly well-off her manual disability had advanced rapidly in connection with the restrictions necessitated by the war conditions. It seems important that in the future due regard is given to the nutritional conditions when analyzing a case of amyotrophic lateral sclerosis; the presence of a severe gastritis may mean something. The matter is another evidence for the importance of a close connection between general medicine and neurology.

Briefly summarizing the discussion it may be said that the following factors are liable to be of importance for the development of amyotrophic lateral sclerosis: --

1. An individual disposition towards abiotrophy of the motor system, as supposed by Spiller and others.
2. An undue strain exerted upon the motor system available, as demonstrated by the present material.
3. A malnutritional factor, possibly represented by vitamin E, as suggested by Einarson and Ringsted (1939).

With regard to the other causes, occasionally accused, the material did not yield any contributions. It is true that in case (2) a traumatic injury did precede the development of the syndrom but although a connection with trauma is suggested by some authors it is difficult to see how such a correlation may be brought about; in cases (1) and (3) no injuries were present. Case (2) was remarkable also with regard to the presence of an extrapyramidal syndrome but since the amyotrophic lateral sclerosis represents an affection of the pyramidal system it is difficult to untangle any correlations, although it may be admitted that a common cause (exertion? deficiency?) may be responsible for both affections (Wimmer has suggested a «chronic encephalitis» as a possible causative agent in amyotrophic lateral sclerosis).

### Summary and Conclusions.

1. Three cases of amyotrophic lateral sclerosis are described, in whom the disease appeared as a complication to a previous long-standing disability of the legs, caused by other disorders (polio-myelitis, malformations).

2. It is suggested that the heavy strain, exerted on the motor system available for use, in order to compensate the immobility otherwise present, may favour the development of amyotrophic lateral sclerosis. This aspect is compatible not only with the apprehension of an abiotrophy but also with the probable importance of a malnutritional factor.

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From the Medical Clinic of the Serafimer Hospital, Stockholm. (Head Physician: Prof. A. Kristenson).

## On Hereditary and Familial Conditions in Gastric Ulcers and Duodenal Ulcers.

By

THOR SÄLLSTRÖM, M.D.

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It has long been observed that gastric ulcers and other gastric diseases are to be found more often in the familial anamneses of ulcer patients than in those of persons with healthy stomachs. The first real investigation into these conditions was published by Plönies in the year 1905. Since then a great deal has been written on the question of the significance of heredity on gastric ulcers and duodenal ulcers. Opinions as to the part played by heredity in ulcer genesis have here proved some what divergent.

Many writers consider it to be established beyond all doubt that hereditary and familial factors play an important part in the occurrence of ulcers (Adler, v. Bergmann and Katsch, Bauer and Aschner, Hutter, Kalk, Mattisson, Nicol, Spiegel, Strauss and others). The hereditary factor is said to lie in the constitution or in a certain condition which is not infrequently observed as a defect in the digestive apparatus (Bauer and Aschner, Kalk, Spiegel).

The data as to how often gastric ulcers are found in the families of ulcer patients vary between 5 and 60 %. Mattisson and Nicol indicate that ulcers in the anamnesis are found twice as often in the case of ulcer patients as in the case of persons with healthy stomachs. Strauss states that they are found in 24 %, Spiegel, Bauer and

Aschner in 26 %. Adler gives the figure as 43 % of ulcer patients but only 5 % of persons with healthy stomachs.

It is natural that the researches into heredity in ulcer cases should show such divergent results. Most of the above-mentioned investigations were carried out before X-ray examination became a regular practice, and therefore it follows that sometimes the diagnoses were certainly not fully reliable. The data obtained from the anamneses must also, of course, in many cases be taken with great reserve.

As evidence in support of the importance of hereditary and familial factors in ulcer genesis, it has been claimed that there are such things as «ulcer families» — i. e. a large number of ulcer cases and other chronic gastric diseases in one and the same family. Such «ulcer families» have not infrequently been described in writings on this subject (Kalk, Lainer, Ritter and Keller, Weidinger, Valle). In a number of cases other factors of importance are then put forward at the same time. For example, v. Bergmann and Katsch speak of vegetative stigmatization, Rossier and Dressler of simultaneous endocrin disorders and Michaelsson of a simultaneous neuropathic affection.

There are, however, authors who deny the importance of hereditary factors in ulcer genesis (Heissen, Lindlau). Heissen finds the familial occurrence of ulcers and gastric diseases among ulcer patients in only 5.5 % and maintains that the exogenous factors are the most important. Lindlau also shows a low proportion — only 3.7 %. Regnbogen has criticized Lindlau's work and has found his examination methods unsatisfactory.

In the study of hereditary conditions from clinical material one must employ the method of deduction or the anamnestic method. One starts here with the patient and tries in one way or another to trace his antecedents. It is quite clear that when one is dealing with a disease like ulcers, it is frequently very difficult to obtain exact information from the anamneses.

The material obtained can then be treated in various ways. The most usual procedure is to work out statistics from the family anamneses that have been obtained and by means of comparison with the normal material, which has been treated in the same way, to form some idea of the effect of heredity. This method has the disadvantage that, particularly if the heredity is of a

recessive type, hospital material of any particular disease is not very representative from the point of view of heredity. Hospital material is somewhat one-sided, in that it only covers the families in which the disease has already manifested itself in one or more individuals, while families that are bearers of similar genotypes, although the genotypes for various reasons do not appear in the generation represented, do not enter the picture. The consequence is that the presence of the hereditary tendency under study in the material examined may appear greater than it actually is. In order to avoid these misleading sources several different statistical methods have been worked out (Weinberg's brother-and sister method, Bauer's and Aschner's compensation and exclusion method). My material is unfortunately not suitable for treatment according to these latter methods but will be treated purely in accordance with the simple statistical-comparative method.

With the object of studying familial and hereditary conditions in ulcers, I have collated ulcer material from the Serafiner Hospital's Medical Clinic covering the years 1936--1942 — in all, 684 cases of gastric and duodenal ulcers. The examination was primarily intended to take the form of a study of the journals, but it soon became clear that, despite the fact that it was a question of using journals kept at a university clinic, the data concerning familial conditions were in many cases totally absent. It therefore became necessary to send out a questionnaire to the patients in order to obtain definite information concerning their anamneses. This questionnaire asked for accurate information concerning gastric ulcers and ulcers in the duodenum and also cancer in the stomach in their families. It was asked *inter alia* whether the patient's relations who had ulcers or cancer had been treated for their complaints at hospital or at home only. The patients were requested also to get their information confirmed by their relations. In 378 cases (approximately 50 %) replies were received to the questionnaire that had been sent out. In a considerable number of cases it appeared that the patients had really taken some trouble over their information and had written round to the whole of their families in order to be able to supply as full and as exact answers as possible. The material received must therefore, in view of the answers, be regarded as satisfactory. This is particularly the case when gastric ulcers have occurred in the anamnesis, where in the great majority

Table 1.

Familial conditions in cases of gastric ulcers.

pgf = paternal grandfather,      mgf = maternal grandfather,  
 pgm = paternal grandmother,    mgm = maternal grandmother.

No. of cases	No known fami- lial case of ulcers	Ulcers in the family													No. of cases of familial ulcers	
		pgf	pgm	mgf	mgm	father	mother	paternal aunts & uncles	maternal aunts & uncles	brother	sister	cousins	own children	brothers		sisters
		a	a	a	a	b	c	d	e	f	g	h	i	j		k
137	88	0	1	0	1	8	9	1	1	13	10	1	2	1	1	49
At the same time as	a						1	1	1	0	0	0	0	0	0	
	b									3	0	0	0	0	0	
	c									1	0	0	0	0	0	
	d										0	0	0	0	0	
	f									1	0	0	1	0	0	
	g									2	2	0	0	0	0	
	h									0	0	0	0	0	0	
	i											1	1	0	0	
Total							1	1	1	7	2	1	2	0	0	

of the cases the relations afflicted with ulcers had been treated at hospitals for their complaints, and in this way of course the suggested diagnoses gained in accuracy. It was not the same as regards the data on cancer of the stomach. Not infrequently the patients merely stated in their replies that someone in their family had died of cancer of the stomach without giving any further particulars. Owing to the unreliability of this information, I have refrained from dealing in my investigation with heredity in the case of cancer.

Tables 1 and 2 show the results of the investigation. The cases are divided into gastric ulcers and duodenal ulcers. I have done this because the writings on the subject contain statements to the effect that gastric ulcers and duodenal ulcers differ as regards familial conditions and that this difference shows a fundamental dissimilarity between the two types of ulcers (Nicol and others). From these tables it can be seen that the familial occurrence of ulcers is at the most 50 % in the case of duodenal ulcers. It seems to be somewhat less in the case of gastric ulcers, where it stands at 36 %.

Table 2.

Familial conditions in cases of duodenal ulcers.  
 pgf = paternal grandfather, pgm = paternal grandmother,  
 mgf = maternal grandfather, mgm = maternal grandmother.

No. of cases		Ulcers in the family															No of cases of familial ulcers
		No known fami- lial case of ulcers															
		pgf a	pgm a	mgf a	mgm a	father b	mother c	paternal aunts & uncles d	maternal aunts & uncles e	brother f	sister g	cousins h	own children i	brothers j	sisters k		
246	123	2	1	1	2	30	17	9	12	28	12	7	2	0	0	123	
At the same time as	a					2	1	2	0	2	0	0	0	0	0		
	b						1	3	1	6	2	0	0	0	0		
	c								3	9	3	0	0	0	0		
	d							2	0	1	1	0	0	0	0		
	e								1	3	1	1	0	0	0		
	f									3	6	0	1	0	0		
	g										2	0	0	1	2		
	h											0	2	0	0		
Total						2	2	7	5	24	15	1	3	1	2		

There is, however, no definite statistical difference between the two types.

In order to obtain material for comparison, I have proceeded in two different ways. In the first place, anamneses with reference to the familial occurrence of ulcers and cancer have been recorded and studied in the case of patients who visited Serafiner Hospital's Medical Polyclinic during September—November 1943, though only, of course, in the case of those who themselves have never had nor been suspected of having ulcers or any chronic gastric disease. In all, 426 patients have been examined for this purpose. This material relating to patients with healthy stomachs comprises both sexes to the same extent and all the adult ages.

In the second place, while on duty at a military hospital, I have had the opportunity of closely studying in the same way the familial conditions of 283 soldiers who themselves have not had any stomach trouble but have for the most part been treated at the hospital for sciatica, affections of the joints, skin and venereal diseases, and whose ages ranged from 20 to 40.



Table 3.

Familial conditions in a normal body of material.  
 pgf = paternal grandfather, pgm = paternal grandmother,  
 mgf = maternal grandfather, mgm = maternal grandmother.

No. of cases	No known fami- lial case of ulcers	Ulcers in the family													No. of cases of familial ulcers	
		pgf a	pgm a	mgf a	mgm a	father b	mother c	paternal aunts & uncles d	maternal aunts & uncles e	brother f	sister g	cousins h	own children i	brothers j		sisters k
709	651	1	0	0	1	18	13	1	0	15	7	2	0	0	0	58
At the same time as	a								1	0	0	0	0	0	0	
	c								0	1	0	0	0	0	0	
	g								1	0	0	1	0	0	0	
Total									2	1	0	1	0	0	0	

The entire material of persons with healthy stomachs comprises, then, 709 cases, of which about 70 % were men, and this corresponds fairly closely with the composition of the ulcer material as regards the sexes.

As to reliability of the material obtained, it should be stated that the information has everywhere been obtained in approximately the same way except for check on the ulcer material by means of the written questionnaire. Gastric ulcers are such a common disease that nowadays most people are familial with it, moreover, during the last 10 or 20 years much has been done in a popular way to improve the public's knowledge on medical questions. Hospital patients in a big city like Stockholm must be fairly well informed on this subject. It has often been stressed that ulcer patients must find it easier to recall cases of gastric and duodenal diseases in their families than other persons with healthy stomachs, and this sounds quite plausible. It seems to me, however, that scarcely anyone who maintains contact with his family would not know about it if a disease such as gastric ulcer were to occur in the family. Moreover, gastric ulcers for the most part require a long stay in hospital and often render the patient incapable of working for a considerable time.

Table 4.

In anamneses of	Both father and mother with ulcers	Father with ulcer	Mother with ulcer	Ulcers in relations of			Own children with ulcers	Brothers and sisters with ulcers	Total
				father and mother	father	mother			
137 gastric ulcer patients .....	0	8	9	0	1	1	2	23	44
246 duodenal ulcer patients .....	1	29	17	0	9	12	2	40	110
Total of 383 ulcer patients .....	1	37	26	0	10	13	4	63	154
709 patients with healthy stomachs	0	18	13	0	1	0	0	22	54

Tables 3 and 4 show the figures for the «normal» material. The difference between the two sets of material is obvious. In only 8.5 % of the cases of persons with healthy stomachs are gastric ulcers found in the family to have occurred. The difference is so great as to be statistically certain. It can therefore be stated that in this investigation the familial incidence of ulcers in the case of ulcer patients is clearly much greater than in the case of other individuals.

A closer analysis of the tables shows that a large number of the ulcer cases are to be found amongst the patients' brothers and sisters. As regards the older generations, no definitely greater incidence of ulcers can be shown here for either the agnates or the cognates. It is sometimes maintained in writings on the subject that the hereditary propensity is transferred by the mother. This is not the case, however, in this material.

In view of statements in the literature on this subject to the effect that patients afflicted with ulcers at an early age almost invariably inherit the disease (von Bergmann and Katsch, Kalk, Mattisson), I have selected patients under the age of 25 from amongst my material, and have collated their familial conditions as regards ulcers (Table 6). It can be seen that out of 11 cases of gastric ulcers within this age group 6 were hereditarily disposed to ulcers, which is equivalent to 55 %, and out of 48 cases of duodenal ulcers 33 showed the familial occurrence of ulcers, which is equivalent to

Table 5.

In familial anamneses are found	In 383 ulcer patients		In 709 persons with healthy stomachs		Difference between frequencies a—b	e (a—b)	$\frac{a-b}{e(a-b)}$
	Frequency % a	its mean error e (a)	frequency % d	its mean error e (a)			
Ulcers . . . .	45 (172)	± 2.5	8.2 (58)	± 1.05	36.8	± 2.7	13.5
Cancer of the stomach	12 (75)	± 1.7	7.4 (52)	± 0.99	4.6	± 1.9	2.42

Table 6.

Familial conditions in ulcer cases under 25 years of age.

pgf = paternal grandfather, pgn = paternal grandmother,  
mgf = maternal grandfather, mgn = maternal grandmother.

No. of cases	No known fami- lial occurrence of ulcers	Ulcers in the family													No. of cases of familial ulcers	
		pgf	pgm	mgf	mgn	father	mother	paternal aunts & uncles	maternal aunts & uncles	brother	sister	cousins	own children	brothers children		sisters children
		a	a	a	a	b	c	d	e	f	g	h	i	j		k
59	18	0	1	1	0	11	6	5	4	7	4	0	0	0	0	39
At the same time as	a						1	1	1	0	0	0	0	0	0	
	b							2	0	0	0	0	0	0	0	
	c								1	1	0	0	0	0	0	
	d							4	1	2	1	0	0	0	0	
	f									0	0	0	0	0	0	
Total							1	7	2	3	1	0	0	0	0	

69 %. This is a higher percentage than for the whole of the material (45 %). The difference is not, however, statistically certain. One indication that the disease in these younger cases are more difficult of prognosis seems to be that patients with gastric ulcers underwent operations for their disease in 25 % of the cases as against 12 % within the whole material, and patients with duodenal ulcers underwent operations in 17 % of the cases as against 8.7 % in the entire material. Moreover, the tendency to a relapse is

unusually great in these young cases, being in the case of gastric ulcers 82 % and in duodenal ulcers 86 %. All the figures must, however, be taken with reserve as the numbers dealt with are quite small.

One factor that is often put forward as evidence of heredity in ulcers is the existence of «ulcer families». In itself this factor does not necessarily indicate heredity, but if an obviously larger number of ulcer families are found in the cases which have had ulcers than in those of persons with healthy stomachs, it must be accorded a certain degree of importance as evidence. Moreover, when a large or moderately large number of cases of the disease occurs in one family, one can probably reckon on obtaining reliable information both from patients amongst the ulcer material and from the normal material.

I have therefore examined the different sets of material to ascertain whether there has been an accumulation of gastric diseases, and have obtained the following results: In the families of patients with gastric ulcers there have been 8 cases of an accumulation of gastric diseases in the family (8 out of 135 cases of gastric ulcers), in the families of patients with duodenal ulcers there have been 21 cases of accumulation of gastric diseases in the family (21 out of 243 cases of duodenal ulcers) and in the families belonging to the «healthy stomach» material there have been 4 cases of accumulation of gastric diseases in the family (4 out of 709 cases of persons with healthy stomachs).

*The normal material:*

- 1) mother ulcer, 2 maternal aunts cancer of the stomach.
- 2) father, brother and a paternal cousin ulcers, paternal grandmother and paternal uncle cancer of the stomach.
- 3) maternal aunt, sister and paternal cousin ulcers, paternal uncle and maternal aunt cancer of the stomach.
- 4) sister ulcer, mother and brother cancer of the stomach.

*Gastric ulcer material:*

- 1) father and one brother gastric ulcers, 2 brothers duodenal ulcers.
- 2) mother and 2 brothers ulcers, brother and sister cancer of the stomach.
- 3) mother and 2 sisters ulcers.
- 4) mother and 4 brothers ulcers.
- 5) maternal aunt and 3 brothers ulcers.

6) paternal grandfather, maternal grandfather and 2 sisters cancer of the stomach.

7) father and mother cancer of the stomach.

8) father, mother and maternal aunt cancer of the stomach.

*Duodenal ulcer material:*

1) maternal grandfather and father duodenal ulcers, paternal uncle ulcer.

2) father and sister duodenal ulcers, brother ulcer.

3) mother, 2 brothers and one sister duodenal ulcers.

4) mother and 4 brothers ulcers.

5) mother, 2 brothers and one sister ulcers.

6) mother, brother and 2 sisters duodenal ulcers.

7) mother and brother gastric ulcers, maternal aunt ulcer.

8) maternal grandmother, mother, brother and sister ulcers, father and paternal uncle cancer of the stomach.

9) mother and 4 brothers ulcers.

10) mother ulcer, maternal grandfather and maternal aunt cancer of the stomach.

11) paternal uncle and 2 brothers ulcers.

12) 2 maternal aunts and brother ulcers, paternal grandmother cancer of the stomach.

13) paternal uncle, maternal aunt and brother ulcers, father and brother gastric trouble.

14) paternal grandmother, paternal uncle and brother ulcers.

15) 3 brothers ulcers.

16) brother and sister ulcers, one sister duodenal ulcer, maternal aunt cancer of the stomach.

17) brother ulcer, maternal aunt and cousin cancer of the stomach.

18) brother and 2 sisters ulcers.

19) brother ulcer, mother and sister cancer of the stomach.

20) mother and brother cancer of the stomach.

Thus, we find a considerable difference between the occurrence of ulcer families in the normal material and that in the ulcer material. If we only count the families in which ulcers are present in the family, the ulcer material shows a frequency of 6.9 % and the normal material a corresponding frequency of 0.57 % ( $d = 6.33 \pm 1.34$ ).

The manifest accumulation of gastric diseases in one and the same family in the case of families belonging to the ulcer material tends to support the importance of the heredity factor in ulcer genesis. It should be noted, however, that in the material described above the preponderance is caused to a certain extent by the accu-

mulation of ulcer cases in the patient's own generation. The fact that in this material we also find ulcers in earlier generations lends support to the heredity factor. If, on the other hand, ulcers only occur, for example, among the patient's own brothers and sisters, the causes may in the main be twofold — hereditary disposition and the fact that the patient and his brothers and sisters have been exposed to the same exogenous conditions. An accumulation of ulcer families in the material need not necessarily, therefore, constitute any proof in support of the heredity factor, but the more generations covered by the ulcer family the more significant must this family become from the heredity aspect.

### Conclusions.

The investigation has shown (1) that gastric ulcers occur far more frequently in ulcer patients' families than in the families of persons with healthy stomachs, and (2) that there is a considerable accumulation of so-called ulcer families in the ulcer material. These circumstances are bound to enhance the importance of hereditary and familial factors in ulcer genesis.

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From the Medical Clinic, University Hospital, Upsala, Sweden.  
Chief: Professor G. Bergmark.

## The »alcacid reaction» — a new qualitative test for serum globulins.

Preliminary report.

By

JAN WALDENSTRÖM.

(Submitted for publication November 17, 1944).

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The investigations of later years have shown that hyperglobulinemia may be a very important symptom both from the practical diagnostical point of view and also theoretically. It has also become clear that hyperglobulinemia is not chiefly a quantitative but also a qualitative problem. One or some of the normal globulin components might be increased or there may even appear a globulin that cannot be traced in normal blood. The closer qualitative and quantitative examination of the serum globulin is no simple task and often requires a complicated and expensive equipment (electrophoresis apparatus, ultracentrifuge). However, it has been found possible with the aid of relatively simple tests to demonstrate that the serum globulins may differ qualitatively in different cases of hyperglobulinemia. Although the chemical or physico-chemical basis of these tests are still only superficially known, they may of course be of a definite practical value.

The simplest of these methods is the dilution reaction, when an euglobulin fraction may be precipitated. A positive result is rare however. Another simple method is the formolgel test. More comp-

licated are the electrophoretic and ultracentrifugal methods of examination that may give invaluable information in selected cases.

A character that is easily determined clinically is an index  $\frac{100 \cdot \eta_{13^{\circ}}}{\eta_{37^{\circ}}}$  (Waldenström 1944), expressing the influence of temperature on serum viscosity. Normally this index lies about 100. In cases with hyperglobulinemia the index may be comparatively high even when the globulin is not maximally increased. On the other hand cases with very high globulin values may have a normal index. It is thus obvious that the temperature index is chiefly a qualitative and not a quantitative character. This is also to a certain extent true of the serum viscosity in itself (Waldenström 1944).

By accident I recently discovered a reaction that does not seem to run parallel with any of the above-mentioned tests. As the technique is simple and the results are obtained very quickly, I shall briefly describe the reaction and discuss a few preliminary results. The future will show if it is of real value. When the diazo reaction is performed it is sometimes of advantage not to make the alcohol precipitation of the proteins as the first stage. A much quicker procedure is to add the diazo reagent to the serum as in the direct reaction and then divide the mixture in two equal parts. To one of these alcohol is added and the development of the typical colour is watched. When performing this reaction on the serum from a patient with liver cirrhosis, I noticed that the serum quickly gelified. The same reaction was later tested on several sera with an increased content of globulin as it was found, that the first patient had a considerable hyperglobulinemia. In all these cases the result was a very quick gelification. I have therefore tried the reaction systematically on a certain number of patients with an increased globulin content of the serum.

The technique for the reaction is the following: To 0.2 ml serum is added 0.2 ml diazo reagent (sulphanilic acid dissolved in hydrochloric acid). 0.2 ml alcohol (96 %) are then added, a stop watch is started and the test tube is briskly shaken two or three times. The test tube is then left alone and is only slightly turned in order to determine the moment of gelification. It is important to await the right moment and not shake the tube too



early. The gelification is regarded as complete if the surface of the gel no longer moves, when the test tube is leaned. Many normal sera give a gelatinous precipitate after more than 90 seconds. The reaction is therefore not to be regarded as positive if it takes more than 90 seconds to develop a gel. I have called it the «alcacid» reaction (alcohol and acid).

The reaction has been modified in several ways without being improved. The addition of a larger amount of acid makes the reaction slower but this cannot be regarded as an advantage. The use of only hydrochloric acid without sulphanilic acid seems to make the gelification less homogenous in certain instances. The diazo reagent has therefore been preferred as it is always at hand in a laboratory. In some rare instances a very firm and quick gelification was noted immediately after the addition of hydrochloric acid without alcohol. It is possible that this is a special feature of some globulin fraction.

As the reaction consists of a gelification of the serum it might be supposed that this is only another way of carrying out the formolgel reaction. I have therefore made both reactions on the same serum. Considerable differences were sometimes found.

On table I are seen the pathological and normal sera arranged according to increasing time for gelification after the addition of formaldehyde. It is seen from the table that both reactions follow each other pretty well in the majority of cases. The chief difference lies in the absolute time for gelification. This is usually much higher in the alcacid reaction. It would naturally have been of a certain importance if there had been a definite parallellism. As it is however the alcacid cannot be regarded only as a modified and quicker formolgel.

The most extreme difference was found in commercial anti-diphtheria serum from a horse with a high globulin content (9%) where 3.5 % was represented by alfa- and 4.4 % was beta-globulin, whereas the gamma-globulin was lower (1.1 %). It showed a negative formolgel reaction (6—8 hours). The alcacid was positive in 5 seconds. In an antitetanus serum the globulin composition was about the same but the content of gamma-globulin was higher (1.7 %). In this serum the formolgel reaction was positive in 105 seconds, the alcacid in 30 seconds. Normal horse serum showed both reactions negative.

Table I.

		Formol-gel	Alcacid sec.	Viscosity		Tot. prot. %	Alb. %	Glob. %	Euglobulin
				37°	13°				
6/8	S. B. Tumor malign.	18"	45			8.08	2.96	5.11	++
15/6	O. F. Myeloma? ....	30"	5	2.6	2.8				—
May	" " ....	60"	17	2.1	2.3	9.2	2.4	6.8	—
18/4	O. K. T.malign.pelvis	28"	25	3.1	3.7				trace
16/3	" " "	33"	36	2.9	3.3				"
8/7	" " "	1'15"	35	2.4	2.7				(+)
15/4	E. E. Myeloma .....	1'30"	19	2.6	2.8				—
22/4	O. W. " .....	1'30"	28	3.3	4.0	12.8	3.5	9.3	trace
	Antitetanus serum ....	1'45"	30	2.6	2.8	9.6	0.9	8.7	—
14/1	O. K. T.malign.pelvis	1'45"	1	2.4	2.6	7.6	3.7	3.9	trace
	B. L. Myeloma .....	1'50"	8					10.2	
1/2	O. W. " .....	2'	23	3.2	3.7	11.95	2.87	8.29	+
24/5	L. E. Lupus erythem.?	2'20"	12	2.5	2.7	10.1	3.8	6.3	trace
17/3	E. E. Myeloma .....	2'20"	22	2.4	2.6				—
18/1	S. F. Cirrh.hep. ....	3'9"	12	1.9	2.0	8.6	3.0	5.6	—
2/2	H. H. Purp.hyperglob.	3'50"	8	2.5	2.7				+
24/5	D. B. Myeloma .....	4'30"	30	3.1	6.4	10.6	3.5	7.9	—
29/5	K. B. " .....	5'	35	2.8	3.0				—
2/4	O. E. Cirrh.hep. ....	6'	45	2.3	2.4	10.1	3.4	6.7	+
19/5	M. A. Chron.arthr.	6'	17	2.5	2.7	10.4	3.6	6.8	—
18/1	S. L. Cirrh.hep. ....	6'50"	15	2.3	2.4	9.61	3.57	6.04	trace
24/5	O. E. " " ....	7'	35	2.2	2.5	10.1	3.8	6.3	"
25/3	I. S. High S.R. ....	8'	21	2.6	2.9	10.35	4.63	5.72	(+)
29/5	W. B. Myeloma? ....	10'	55	2.6	2.9				+
12/8	P. G. ? ....	10'	—	2.6	2.7				—
15/4	S. E. High S.R. ....	20'	30	2.1	2.3	9.29	4.18	5.11	—
15/12	" " " ....	28'	23	2.2	2.2				trace
29/5	L. B. " " ....	54'	45	2.8	3.0				—
20/5	E. E. Myeloma .....	60'	—	2.1	2.2				—
20/1	A. L. Purp.hyperglob.	60'	20	2.2	2.4				—
16/5	" " "	80'	—	2.1	2.2	9.1	4.2	4.9	(+)
	Antidiphtheria serum I ....	6—8 h.	5	2.8	3.2	10.3	1.3	9.0	—
	Antidiphtheria serum II ....	4 h.	30						—
10/1	G. L. Hodgkins disease	—	30	2.1	2.1				—
31/1	A. P. High S.R. ....	—	40	2.0	2.0				—

There are also some sera, where both reactions are very quick even if this is quite uncommon. It was found in one person with a very peculiar protein pattern in the serum probably caused by an abnormal fibrinogen.

It is naturally too early to judge the value of the reaction. As it is the possibilities to differentiate the globulins are not very numerous and it seems important to find simple reactions that might possibly correspond to definite globulin fractions.

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Aus der Lungentuberkuloseabteilung des Universitätskrankenhauses in Uppsala, Schweden. (Chefarzt: Dozent E. Hedvall).

## Säurefeste Saprophyten, eine wichtige Fehlerquelle bei der Tuberkulosedagnostik

von

ERIK HEDVALL.

(Bei der Redaktion am 16. November 1944 eingegangen).

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In neuerer Zeit ist Tuberkelbazillenzüchtung von Sputum, Ventrikelspülflüssigkeit und anderem Material an unseren bakteriologischen Laboratorien, Sanatorien und Krankenhäusern immer gewöhnlicher geworden. Diese Entwicklung muss als glücklich betrachtet werden, da die Methode einen sehr hohen Wert besitzt. Die Züchtung liefert jetzt mindestens ebensooft positive Resultate wie Meerschweinchenproben und stellt sich ausserdem erheblich billiger als diese. Das Verfahren hat jedoch den wesentlichen Nachteil, dass es das Vorhandensein von Tuberkelbakterien nicht beweist. Die auswachsenden Bakterien können nämlich säurefeste Saprophyten sein, welche ebensowenig wie die Tuberkelbazillen durch die Säurebehandlung zerstört werden, die der Aussaat auf dem Substrat vorhergeht. Nur durch ergänzende Meerschweinchenprobe kann man Aufschluss hierüber erhalten.

Die Mehrzahl der Heilstättenärzte, die sich mit Züchtung beschäftigen, sind wohl der Ansicht, dass die säurefesten Saprophyten keine Rolle bei der Tuberkulosedagnostik spielen. Aber ist diese Auffassung richtig? Säurefeste Saprophyten kommen doch sowohl ausserhalb als innerhalb des menschlichen Körpers vor,

weshalb die Möglichkeit einer Verwechslung nicht ohne weiteres von der Hand gewiesen werden kann. Ich verweise hier auf Tab. 1, die Eichbaum's ausgezeichneten Zusammenstellung »Die tuberkelbazillenähnlichen, säurefesten Saprophyten« von 1933 entnommen ist.

Die Richtigkeit des Obigen geht auch aus anderen Untersuchungen hervor, von denen ein Teil aus neuerer Zeit stammt. Husted hat bei mikroskopischer Untersuchung säurefeste Saprophyten in folgenden Fällen nachgewiesen:

1) Harn eines 37jährigen Mannes.

Bei mikroskopischer Untersuchung wurden einzelne säure- und alkoholfeste tuberkelbazillenartige Stäbchen festgestellt. Meerschweinchenprobe und Züchtung auf Petroffs Substrat fielen negativ aus. *Die klinische Diagnose war Nephrolithiasis.* Keine Zeichen von Tuberkulose. Keine Albuminurie oder Pyurie.

2) Katheterharn eines 10jährigen Mädchens.

Im Laboratorium des Krankenhauses wurden in frischen Harnproben zweimal säurefeste Stäbchen und im Katheterharn einzelne tuberkuloseverdächtige Bazillen angetroffen. Kein Wachstum bei Züchtung auf Agar. Im Staatlichen Seruminstitut in Kopenhagen wurden im Katheterharn säure- und alkoholfeste Stäbchen konstatiert, aber sowohl Meerschweinchenprobe wie Kultur auf Petroff's Substrat hatte negatives Ergebnis. *Die klinische Diagnose war Nephritis haemorrhagica.* Keine Zeichen von Tuberkulose. Cystoskopie ohne Befund. Nierenröntgen normal.

3) Harn einer Frau.

Im Tagesharn wurden eine Anzahl säure- und alkoholfeste, tuberkelbazillenartige Stäbchen angetroffen, die jedoch eine etwas helle Farbe hatten. Züchtung auf Petroff's Substrat ergab kein Wachstum. Ein Meerschweinchen, das mit dem Harn geimpft wurde, starb vorzeitig infolge einer anderen Ursache. Im Katheterharn wurden eine Anzahl säure- und alkoholfeste, tuberkelbazillenartige Stäbchen nachgewiesen. Meerschweinchenprobe und Kultur auf Petroff's Substrat fielen negativ aus. *Die klinische Diagnose war Cystitis.* Zeichen von Tuberkulose waren nicht zu bemerken. Die Pyurie und die Albuminurie verschwanden.

4) Harn eines 13jährigen Mädchens.

Im Nachverlauf nach einer Appendektomie entstand Hämaturie. Im Katheterharn wurden säurefeste, ganz an Tuberkelbazillen erinnernde Stäbchen festgestellt. Der Harn wurde an das Staatliche Seruminstitut gesandt, wo man indes weder bei Mikroskopie, Züchtung noch Meerschweinchenprobe Tuberkelbazillen entdecken konnte. In einer später eingeschickten Harnprobe fand man indes einige säure- und alkoholfeste Stäbchen,

Tabelle 1.

Vorkommen	Autor
1. In der unbelebten Natur und im Pflanzenreich.	
Erde	Herr, Kersten, Söhnlein, Vierling, Frey und Hagan, Büttner, G. Seiffert
Leitungswasser (Ausflusshähne; Gummi- und Glasansätze an den Wasserhähnen, zentrale Rohrleitungen; Brunnen; Hochwasserbehälter)	Barraunikow, Brem, Beitzke, McFarland, Burville-Holmes, Beardsly, Case, Schern und Dold, B. Lange Maie, Heymann und Seidel, Eichbaum
Destilliertes Wasser	Brem, V. Lehmann, Burville-Holmes, McFarland, Beardsly, Case
Gullyschlamm, Abwasser	B. Lange, Abel
Süss- und Salzwasserbehälter, Froschbehälter, Aquarien	Barrannikow Poscharyski, Weber und Taute
Gräser, Grassamen, Getreidekörner, Heu, Heustaub	Moeller, Herr, Happich, Dieudonné und Lubarsch
Strassenstaub, Sägespäne	Happich
Staub von Tierställen	Brem, Schwabacher
Wohnungstaub, »Luftstaub«	Eichbaum
Moos	Weber und Taute
Torf	Büttner
Rüben	Bugge und Kiesig
Kinderspiel-Sandhaufen	Moeller
Konserven	Townsend
Trompeten (»Blech«- und Holzblasinstrumente)	Jakobitz und Kayser, Heymann und Seidel, B. Lange, Schmitz, Merten, Eichbaum
2. Bei Tieren und in tierischen Produkten.	
Normale Frösche	Weber und Taute, B. Lange
Normale Kaninchen (Venenblut)	Schwabacher, Bacmeister
Innere Organe normaler Meerschweinchen (bei Rübenfütterung)	W. Seiffert
Fliegen	Hohn
Smegma praeputii von Rindern	Neufeld

V o r k o m m e n	A u t o r
Präputialdrüsen einer Ratte	Galli-Valerio
Anel- und Scheidengegend von Kühen, Meerschweinchen, Hunden, Ratten	Cowie
Mageninhalte von Kühen	Büttner
Mist, Dung, Tierkot	Severin, Capaldi, Ferran, Olt, Moeller, Herr, Bertani, Kroeger
Milch, Butter	Rabinowitsch, Petri, Tobler, Hor- mann und Morgenroth, Carnevali, Hess, Kaiser
Huhn: Kloake, Eileiter, Ei	Klimmer, Knorr
Mammapfropf einer milchenden Kuh	Neufeld
Mastitis bei einer Kuh	De Jong
Abszessleiter bei einer Kuh (*Pseudo- perlsucht*)	Moeller
3. Beim Menschen und in menschlichem Untersuchungsmaterial.	
a) Beim Gesunden.	
Smegma (Präputium, Vulva, Analfal- ten)	Alvarez und Tavel, Matternstock, Klemperer, Lenhartz, Abel, Laser, Czaplewski, Neufeld, Bitter, C. Fraenkel, Gottstein, Bienenstock, Weber und Trannenroth, Weber, Laabs, Dahms, Brereton und Smitt, Young und Churchman
Haut (Achselgefalte, Zwischenzehenfal- ten, Nabelgrube, Ellenbeuge, Knie- kehle)	Matternstock, Moeller, Eichbaum
Urin	Marpman, Laser, Laabs
Stuhl	Mironescu, Ferran und Strasburger
Nasenschleim	Karlinski, Laabs
Mundhöhle (Zunge, Tonsille bezw. Mandelpfröpfe, Zahnbelag)	Moeller, Laabs, Rorida und Simonl, Marzinowski, Beck, Molly, G. Mayer

Vorkommen	Autor
Blut	Popper, Bodart und Schindler, Schwabacher, E. Loewenstein (Torri)
Cerumen	Gottstein, Laabs, Bitter
Mund, Augen, Nasenwinkelsekret (Comedonen)	Laabs
b. Beim Kranken.	
Sputum bei Bronchitis	Moeller, Ohlmacher, Lichtenstein
Sputum bei chronischer Lungenerkrankung nach Kampfgasvergiftung	Nègre, Valtis und Labernadie
Lungengangrän und Lungenabszess	Pappenheim, A. Fraenkel, Rahinowitsch, Folli
Bronchiektasien	Cutmann
Chronische Bronchopneumonie	Birt und Leischmann, Ophüls
Eiter bei Otitis media	De Simoni
Abszesseiter (Spritzenabszess)	Bruynoghe und Adant
Beckenabszesseiter	Mayer
Ozaena	Alexander
Rückenphlegmone bei Decubitus Appendicitis Mesenterialeyste	Bender
Ovarialeyste mit Fistelöffnung in den Darm	Dietrich
Pleuraexsudat	Moeller, Beaven und Bayne-Jones
Talgdrüsenepitheliom Carcinome und Sarkome	Mezinescu
Acne conglobata	Pick
Blut bei Tuberkulösen	Rabinowitsch, Saenz
Blut bei Chorioretinitis	Tiedemann
Blut bei Leichen (ohne Tuberkulose)	Popper, Bodart und Schindler
Leichenorgane bei Miliartuberkulose (Milz, Krebsmetastasen)	Harvey Pirie



die jedoch bei Züchtung und Meerschweinchenprobe negative Resultate gaben. Klinisch waren keine Zeichen von Tuberkulose nachweisbar. Pirquet's Reaktionsprobe, die wiederholt, das letzte Mal unmittelbar vor den erwähnten Harnuntersuchungen, stattfand, fiel negativ aus. Röntgenphotographie von Thorax, Abdomen und Nieren zeigte normale Verhältnisse.

#### 5) Harn eines 40jährigen Mannes.

Bei Harnuntersuchung wurden zweimal säure- und alkoholfeste Stäbchen festgestellt, die völlig mit Tuberkelbazillen übereinstimmten. Katheterharn und Urin aus den Ureteren enthielt dagegen keine Tuberkelbazillen. Meerschweinchenprobe mit Ureterharn fiel negativ aus. Bei Untersuchung im Staatlichen Seruminstitut wurden weder bei Mikroskopie, Züchtung noch Meerschweinchenprobe Tuberkelbazillen im Harn angetroffen. *Klinische Diagnose: Nephrolithiasis. Malformatio pelvis renis sin.* Bei Cystoskopie zeigte sich die Schleimhaut in der Pars prostatica etwas gerötet und injiziert, war aber sonst ganz normal. Die Uretermündungen waren normal. Bei Pyelographie wurde ein linksseitiges doppeltes Nierenbecken konstatiert, in dessen einem Teil sich zwei sichere erbsengrosse Steinschatten fanden.

#### 6) Spinalflüssigkeit eines 5jährigen Mädchens.

Bei Mikroskopie wurden zahlreiche säure- und alkoholfeste Stäbchen beobachtet, die völlig das Aussehen von Tuberkelbazillen hatten. Züchtung auf Petroff's Substrat fiel negativ aus. Das Meerschweinchen, welches geimpft wurde, starb nach 12 Tagen an Pasteurellose. Bei der Sektion war keine Tuberkulose nachweisbar. *Die klinische Diagnose war Meningitis serosa.* Alle klinischen Erscheinungen von Meningitis lagen vor. Bei der ersten Lumbalpunktion war der Druck 250 mm, Zellen 1280/3, Globulin 3 und Albumin 20. Mikroskopisch waren nach einfacher Färbung oder nach Züchtung keine Bakterien nachweisbar. Pirquet neg. Ophthalmoskopie o.B. Pat. wurde nach zweimonatiger Behandlung aus dem Krankenhaus entlassen und befand sich ein halbes Jahr später bei guter Gesundheit.

#### 7) Spinalflüssigkeit eines Knaben.

Bei mikroskopischer Untersuchung wurden zahlreiche säure- und alkoholfeste, sehr polymorphe Stäbchen angetroffen, von denen ein Teil ganz an Tuberkelbazillen erinnerte. Züchtung und Meerschweinchenprobe fielen negativ aus. *Die klinische Diagnose war Encephalitis. Sequelae.* Keinerlei klinische Zeichen von Meningitis. Wurde nach langer Krankenhausbehandlung unge bessert entlassen.

#### 8) Pleuraflüssigkeit eines 64jährigen Mannes.

Bei mikroskopischer Untersuchung von Pleuraflüssigkeit wurden einige säure- und alkoholfeste, tuberkelbazillenartige Stäbchen festgestellt. Züchtung und Meerschweinchenprobe fielen negativ aus. *Klinische Diagnose: Gangraena pulmonum. Pleuritis septica.* Pat. starb. Keine Sektion.

Diese Fälle zeigen, dass Saprophyten, die ganz Tuberkelbazillen gleichen, bei krankhaften Zuständen im menschlichen Körper vorkommen und die Diagnostizierung erschweren können. Husted unterstreicht besonders, dass es nicht ratsam ist, die Diagnose Tuberkulose lediglich auf Grund säurefester Bazillen im Harn zu stellen, die man bei mikroskopischer Untersuchung beobachtet hat.

Hedvall hat 1933 über 2 Fälle von säurefesten Saprophyten berichtet, die bei Lungenkrankheiten nachgewiesen wurden. In beiden Fällen konnten die Bakterien reingezüchtet werden und waren apathogen für Meerschweinchen.

Der eine Fall war ein Mädchen mit kongenitalen Bronchiektasien. Pat. war vorher wiederholt in einem Sanatorium unter der Diagnose Lungentuberkulose behandelt worden. Nach Aufnahme in die Abteilung für medizinische Tuberkulose des St.-Göran-Krankenhauses konnte man mit Bronchographie feststellen, dass die ganze rechte Lunge von verschieden-grossen Hohlräumen durchgesetzt war. Die linke Lunge war dagegen gesund. In wiederholten Sputumproben waren keine Tuberkelbazillen nachweisbar. Bei Züchtung von Sputum nach Hohn's Methode erhielt ich indes Kolonien, die sowohl in ihrem makroskopischen Aussehen als in bezug auf Form und Färbbarkeit völlig mit gewöhnlichen säurefesten Tuberkelbazillen übereinstimmten. Eine Aufschlammung der Bakterien wurde Meerschweinchen eingespritzt, bei denen indes keine tuberkulösen Veränderungen auftraten. Dass man es hier mit Saprophyten zu tun hatte, war damit ziemlich sicher bewiesen, da die Bakterien in sehr grosser Menge eingespritzt worden waren, ging aber auch aus dem späteren Verlauf hervor. Um die Kavernen zum Zusammenfall zu bringen, wurde auf der rech'en Seite zuerst eine Phrenicoexzese vorgenommen, der nach einiger Zeit eine totale Plastik folgen sollte. Pneumothoraxbehandlung war nämlich wegen ausgebreiteter Verwachsungen zwischen Lungen und Brustwand nicht möglich. Pat. überstand den Eingriff gut, wollte aber vor der Plastikoperation erst für einige Zeit nach Hause zurückkehren. Dort starb sie indes plötzlich infolge einer sehr starken Lungenblutung. Bei der Sektion konnte man die ausgedehnten bronchiektatischen Veränderungen feststellen, aber keine Lungentuberkulose. Die durch Züchtung von Sputum erhaltenen säurefesten Bakterien, die in Form und Färbbarkeit völlig mit gewöhnlichen Tuberkelbazillen übereinstimmten, waren also nur säurefeste Saprophyten.

In dem zweiten Fall handelte es sich um eine Frau, die gleichfalls lange und wiederholt in einem Sanatorium unter der unrichtigen Diagnose Lungentuberkulose behandelt worden war. Bei Kontrastfüllung der Bronchien wurden doppelseitige, überwiegend linksseitige, sackförmige Bronchiektasien nachgewiesen. Da Pat. sehr an ihrer Krankheit litt, machte ich einen Versuch mit linksseitiger Pneumothoraxbehandlung, weil die Säcke

auf dieser Seite am grössten waren. Das Resultat war gut, Pat. war dann mehrere Jahre fieberfrei und hatte nur geringe Beschwerden von ihrer Krankheit. Vor der Anlegung des Pneumothorax hatte man niemals Tuberkelbazillen im Sputum nachweisen können. Als nach Einleitung der Behandlung die Hohlräume zusammenzufallen begonnen hatten und also ihren Inhalt besser als vorher entleerten, traten indes im Sputum säurefeste Stäbchen von für Tuberkelbazillen völlig typischem Aussehen in so grosser Menge auf, dass man gleichsam einen roten Teppich unter dem Mikroskop sah. Die Bakterien erwiesen sich bei näherer Prüfung als säurefeste Saprophyten ohne meerschweincheninfizierende Eigenschaften. Alle drei vorgenommenen Meerschweinchenproben zeigten nämlich keine tuberkulösen Veränderungen.

Aus den beiden hier mitgeteilten Fällen geht hervor, dass bei Bronchiectasien der Nachweis säurefester Stäbchen im Sputum nicht genügt, um die Diagnose Tuberkulose stellen zu können. Meerschweinchenproben sind in solchen Fällen immer notwendig, da man nur durch sie entscheiden kann, ob die säurefesten Stäbchen pathogen sind oder nicht, m. a. W., ob sie Tuberkelbazillen sind oder nur säurefeste Saprophyten.

Lester hat 1938—1939 einen wertvollen Beitrag zu der Frage des Vorkommens säurefester Saprophyten geliefert. Im Staatlichen Seruminstitut in Kopenhagen wurden 1932—1936 insgesamt 26343 eingesandte Proben auf Tuberkelbazillen untersucht. Hierbei konnten nicht weniger als 130 Stämme von säure- und alkoholfesten Saprophyten reingezüchtet werden (0.5 %), woraus deutlich hervorgeht, wie vorsichtig man bei der Beurteilung des bei Züchtung erzielten Wachstums sein muss (Tab. 2). Der Verfasser gibt in seiner Arbeit eine eingehende Beschreibung der bakteriellen Eigenschaften dieser Stämme. Die Bakterien wurden meist bei Züchtung von Ventrikelspülflüssigkeit erhalten.

Gellerstedt hat kürzlich über 7 Fälle einer eigentümlichen Hautkrankheit berichtet, die in diesem Zusammenhang von Interesse ist. Die Krankheit wird als eine Ulceration der Haut charakterisiert, die im allgemeinen auf den Extremitäten lokalisiert ist, oft in der Nähe der grossen Gelenke. In der Regel kommt auch regionäre Lymphombildung vor. Der Verlauf ist gutartig, ohne Rezidiv. Das histologische Bild erscheint tuberkuloid und zeigt in typischer Weise grosse, unscharfe, käsige und käsig-eitrige Nekrosen sowie reine Eiterherde. Voluminöse Bazillenmassen kommen in allen Fällen vor. Die Bazillen unterscheiden sich in vieler

Tabelle 2.

Jahr	Das Material, von dem die Saprophyten reingezüchtet wurden						Gesamt- zahl der Züch- tungs- proben
	Ventrikel- spülflüs- sigkeit	Ex- pektorat	Pleura- flüssigkeit	Harn	Anderes Material	Insgesamt	
1932—33	6	3	1	1	1	12	8018
1934....	19	3	2	4	4	32	4807
1935....	23	3	3	4	5	38	5939
1936....	27	4	1	15	1	48	7579
Insgesamt	75	13	7	24	11	130	26343
Prozent ..	57.7	10.	5.4	18.4	8.5		

Beziehung von Tuberkelbazillen, vor allem durch ihre geringere Grösse, ihren Pleomorphismus, die Tendenz zu bündelförmiger Gruppierung und durch Bildung von intrazellulären Bazillenkugeln (Globi). Die Art der Bakterien ist vorläufig unbestimmbar, da Kultur- und Impfungsversuche bis jetzt negativ ausfielen. Gellerstedt weist auf die Gleichheit der Krankheit mit den sog. »skin lesions in tuberculinreacting cattle« hin, ferner diskutiert er eine Infektion mit zufällig pathogenen säurefesten Saprophyten der Aussenwelt.

Aus dem Obigen geht hervor, dass säurefeste Saprophyten beinahe überall, sowohl ausserhalb als innerhalb des menschlichen Körpers, vorkommen und dass sie eine wichtige Fehlerquelle bei der Tuberkulosedagnostik sein können. Dies ergibt sich auch aus meinen eigenen Untersuchungen, über die ich im folgenden berichten will.

In der Zeit vom Mai 1943 bis zum August 1944 wurden im Zentralsanatorium in Uppsala insgesamt 1654 Züchtungen mit Material von Tuberkulosepatienten vorgenommen. Von diesen ergaben 420 Kulturen humanes und 3 bovines Wachstum. Bei 10 Kulturen wurde Wachstum säurefester Saprophyten erhalten, bei 6 Wachstum von nicht säurefesten Kokken und Stäbchen sowie von säurefesten Kokken und einzelnen kurzen säurefesten Stäbchen, die zwar schwachen Verdacht auf Tuberkelbazillen weckten, aber

meerschweinchenapathogen waren. Die letztgenannten sind nicht in Tab. 3 aufgenommen, obgleich auch sie säurefeste Saprophyten sein dürften, da die säurefesten Stäbchen so sparsam vorkamen. Die übrigen 1215 Kulturen ergaben keinerlei Wachstum.

Da die Bereitung des Substrats und die Ausführung der Züchtung von Bedeutung für die Entstehung von Verunreinigungen in Form säurefester Saprophyten sein kann, will ich hier kurz die angewandte Methodik beschreiben, die übrigens die gebräuchlichste sein dürfte.

*Substratbereitung (Löwensteinsubstrat):* Für das Substrat ist eine Salzmischung, eine Eimischung und eine Farblösung erforderlich. Die *Salzmischung* (1.2 g Monokaliumphosphat, 0.12 g Magnesiumsulfat, 0.3 g Magnesiumzitrat, 1.8 g Asparagin und 15 g Glyzerin in 300 g destilliertem Wasser) wird eine halbe Stunde gekocht. Nach Abkühlung der Mischung werden 15 g Kartoffelmehl zugesetzt. Hierauf wird sie in ein anfangs kaltes Wasserbad gebracht. Dieses wird unter ständigem Schütteln auf 100° erwärmt, worauf ca. 15 Min. langes Kochen erfolgt. Um sichere Sterilität zu gewährleisten, kocht man die Salzmischung auch während der beiden folgenden Tage jedesmal 15 Min. *Eimischung:* 12 gut gereinigte Eier werden eine halbe Stunde in 96 %igem Alkohol aufbewahrt und dann mit sterilen Handschuhen herausgenommen. Um zu kontrollieren, dass die Eier frisch sind, schüttet man den Inhalt jedes Eies erst in ein kleineres, steriles Gefäß und dann alle Eier in ein größeres. Die Eier werden mit einem sterilen Glasstab unter solchen Verhältnissen gerührt, dass keine Verunreinigung durch Luftbakterien stattfinden kann. Die *Farblösung* (2 %ige Malachitgrünlösung) wird in der Weise bereitet, dass man den Farbstoff erst auf sterilem Papier abwägt und dann in sterilem, destilliertem Wasser löst. Hierauf wird die Mischung 2 Tage je eine halbe Stunde in strömendem Dampf erhitzt.

Zu 300 g Salzlösung werden 500 g Eilösung gesetzt und dann langsam unter ständigem Umschütteln 10 cm<sup>3</sup> 2 %ige Malachitgrünlösung. Als dann wird die Mischung durch ein Gazegewebe in einem Trichter (die Trichtermündung ist mit Gummischlauch, Glasmundstück und Klemme versehen) direkt in Reagenzröhrchen filtriert, die mit Watte verschlossen werden. Alles hierzu erforderliche Material ist natürlich im voraus sterilisiert. Die Röhrchen werden in halbliegender Stellung in einen Trockensterilisator gesetzt und eine Stunde bei 90° erhitzt. Wenn die Röhrchen abgekühlt sind, werden die Pfropfen paraffiniert, worauf man die Sterilität des Substrats dadurch prüft, dass man die Röhrchen 2 Tage bei 37 in einem Thermostaten aufbewahrt.

*Züchtungsmethode:* Sputum und 9.2 %ige Schwefelsäure im Verhältnis 1:4, aufbewahrt in Schüttelröhrchen (220 × 20 mm) mit eingeschliffenen Stöpsel, werden 5—10 Min., oder bis man volle Emulsion erhalten hat kräftig in einer Schüttelmaschine geschüttelt. Nachdem die Säure 15 Min

auf das Sputum eingewirkt hat, wird die Sputum-Säure-Mischung 5 Min. stark zentrifugiert. Der Säuregehalt des Sediments wird durch Zusatz von 1—2 Tropfen 4 %iger NaOH vermindert, worauf die Anssaat des Sediments in 3 Substratröhrchen erfolgt. Bei Züchtung von Ventrikelspülflüssigkeit oder Harn verfährt man in derselben Weise, doch muss die Flüssigkeitsmenge vorher konzentriert werden. Die Ventrikelspülflüssigkeit wird 15 Min. mit 9.2 %iger Schwefelsäure behandelt, während Harn eine Säurebehandlung von 30 Min. erfordert. Pleuraexsudat wird erst kräftig zentrifugiert, worauf man das Sediment abermals in ca. 1 cm<sup>3</sup> neuem Exsudat aufschlämmt. Die Säurebehandlung muss ca. 20 Min. dauern.

Säurefeste Saprophyten wurden also bei Züchtung in 10 von 1654 Proben nachgewiesen, entsprechend ungefähr 0.6 %, was eine bemerkenswert hohe Ziffer ist. Die 10 Züchtungen fanden bei ebenso vielen Patienten statt, nämlich in 1 Fall von Tbc. lymphogland. hili et mediastini (Tbc. primaria), 1 Fall von Pleuritis exsudat. + Tbc. pulm. levis und in 8 Fällen von Tbc. pulm. Da es von Interesse sein dürfte zu erfahren, welche Folgen eine Fehlbeurteilung der säurefesten Saprophyten hatte oder gehabt haben könnte, will ich im folgenden über die 10 Fälle berichten, die in Tab. 3 zusammengestellt sind.

#### Fall 1. 16jähriges Mädchen.

Keine Tuberkulose in der Familie. Anfang April 1943 erkrankte Pat. mit den gewöhnlichen Erscheinungen von linksseitiger Pleuritis. Pat. wurde am 16.4. in die Medizinische Universitätsklinik aufgenommen, von wo sie am 14.5. in das Zentralsanatorium in Uppsala verlegt wurde. Thoracocentese bei 4 Gelegenheiten, wobei insgesamt 1970 cm<sup>3</sup> Exsudat herausgeschafft und mit Luft ersetzt wurden. Die Gasbehandlung wird noch fortgesetzt. Die linke Lunge ist röntgenologisch frei von Veränderungen, die rechte weist in der rechten Sel eine unbedeutende Fleckigkeit von tuberkulöser Natur auf. Tuberkulinreaktion positiv. Mikroskopische Untersuchung von sämtlichen 26 Sputumproben fiel negativ aus, ebenso Kultur auf Ventrikelspülflüssigkeit und Sputum. Züchtung von frisch abgezapfter Pleuraflüssigkeit ergab indes Wachstum säurefester Stäbchen von etwas wechselnder Länge. Zwei Meerschweinchen, die mit Material von der Kultur geimpft wurden, fielen negativ aus, weshalb also die säurefesten Bakterien Saprophyten waren.

Diagnose: Pleurit. exsudat. sin. + Tbc. pulm. dxt. levis. Der Befund säurefester Saprophyten hat in diesem Fall nur beschränktes Interesse, da eine Fehlbeurteilung der Bazillen die Behandlung nicht beeinflusst hätte.

## Fall 2. 33jährige Frau.

Behandlung im Sanatorium Söderby vom April 1935 bis zum Oktober 1936 unter der Diagnose Tbc. pulm. + Stat. post. pnth. art. sin. et thoracoplast. Plastikoperation im Januar und März 1936. Sputum bei der Aufnahme tbb +, bei der Entlassung tbb —. Kontrolliert in der Zentrallungenfürsorgestelle in Uppsala seit Januar 1941. Sämtliche Röntgenbilder zeigten dasselbe Bild: gut ausgeführte Plastikoperation auf der linken Seite. In den sichtbaren Teilen der linken und in der ganzen rechten Lunge keine Zeichen von aktiver Lungentuberkulose. Die Tuberkulinreaktion war positiv. Kultur von Sputum im September 1941 negativ. Bei erneuter Züchtung von Ventrikelspülflüssigkeit im Juni 1943 erhielt man Wachstum säurefester tuberkelbazillenartiger Stäbchen. Zwei Meerschweinchenproben wurden mit Kulturmateriel vorgenommen. Beide fielen negativ aus. Also waren die Bazillen säurefeste Saprophyten.

Diagnose: Tbc. pulm. sin. (sanata). Stat. post thoracoplast. In diesem Fall hätte eine Fehldeutung der Bazillen neue Sanatoriumbehandlung und unnötige Massnahmen zwecks Verhinderung von Ansteckung der Umgebung zur Folge haben können. Nachdem man festgestellt hatte, dass die Bakterien nur säurefeste Saprophyten waren, erhielt Pat. ein Zeugnis für Aufnahme in die Krankenkasse, das sie sonst in vielen Jahren nicht bekommen hätte.

## Fall 3. 48jährige Frau.

Wegen Lungentuberkulose des Sohnes wurde Pat. im Mai 1943 in der Zentrallungenfürsorgestelle in Uppsala untersucht. Dabei konstatierte man röntgenologisch einen rundlichen, gut abgegrenzten und fast kalkdichten Fleck hinter dem rechten C<sub>7</sub>. In der Umgebung desselben fanden sich kleine kalkdichte Flecken. Ausserdem sah man einen linksseitigen Pleuritisrest. Tuberkulinreaktion positiv. Bei Sputumzüchtung erhielt man Wachstum von dicken, kurzen, säurefesten Stäbchen. Zwei Meerschweinchen, die mit Material von der Kultur geimpft wurden, reagierten indes negativ, weshalb also säurefeste Saprophyten vorlagen. Der Lungenzustand war bei wiederholten Röntgenphotographien unverändert. Zeichen von aktiver Tuberkulose liegen nicht vor. Erneute Sputumzüchtung fiel negativ aus.

Diagnose: Tbc. pulm. dxt. inveterat. (sanata ?) + Seq. pleurit. sin. Fehlbeurteilung der säurefesten Stäbchen hätte hier unnötigen Sanatoriumaufenthalt und Massnahmen zur Verhinderung von Ansteckung zur Folge haben können.

## Fall 4. 32jähriger Mann.

Bei Schirmbilduntersuchung im Mai 1943 konstatierte man in der rechten Spitze (ScI—II) äusserst zahlreiche Stränge und Flecken, von

denen die Mehrzahl kalkdicht war. Die Veränderung machte bei näherer Untersuchung nicht den Eindruck, in Gang befindlich zu sein. Tuberkulinreaktion positiv. Züchtung von Ventrikelspülflüssigkeit ergab indes in einem Röhrchen reichliches Wachstum von nicht säurefesten Stäbchen und Kokken sowie ziemlich reichliches von säurefesten Stäbchen und Kokken. In einem andern Röhrchen fanden sich teils ziemlich dicke säurefeste Stäbchen, teils einzelne nicht säurefeste. Inhalt jedes der beiden Röhrchen wurde auf zwei Meerschweinchen verimpft. Sämtliche Meerschweinchenproben fielen negativ aus. Die Lungenveränderungen wurden kontrolliert und weisen nach wie vor keine Zeichen von Aktivität auf.

Diagnose: Tbc. pulm. dxt. inveterat. (sanata?). Fehlbeurteilung der säurefesten Stäbchen hätte unnötige Sanatoriumbehandlung und Massnahmen zur Verhütung von Ansteckung zur Folge haben können.

#### Fall 5. 4-jähriger Knabe.

Tuberkulose in der Familie. Im Zusammenhang mit der Erkrankung eines Verwandten an Tuberkulose konstatierte man bei dem Patienten eine linksseitige Hili- und Mediastinaldrüsentuberkulose. Wurde deshalb vom Juni 1943 bis zum Januar 1944 im Zentralsanatorium in Uppsala behandelt. Tuberkulinreaktion positiv. Bei Züchtung von Ventrikelspülflüssigkeit erhielt man Wachstum stark tuberkelbazillenartiger Stäbchen, aber Verimpfung des Wachstums auf zwei Meerschweinchen hatte negatives Ergebnis.

Diagnose: Tbc. lymphogland. hili sin. et mediastini. (Tbc. primaria). Das Vorhandensein säurefester Saprophyten ist in diesem Fall nur von beschränktem Interesse. Pat. hatte zweifellos eine in Gang befindliche Tuberkulose und wurde wegen dieser Krankheit behandelt. Die Behandlung wäre dieselbe gewesen, wenn man die Bazillen fehlbeurteilt hätte.

#### Fall 6. 34-jährige Frau.

Tuberkulose in der Familie. Im Juni 1943 wurde rechtsseitige Lungentuberkulose konstatiert. Aufnahme in das Zentralsanatorium in Uppsala am 3.7. Zentral in der rechten Lunge fand sich eine wolkige, ungefähr handtellergrosse Verdichtung. Die Tuberkulinreaktion war positiv. Das Sputum enthielt Tuberkelbazillen in mässiger Menge. Am 8.7. wurde rechtsseitiger Pneumothorax angelegt und dann ohne Komplikationen beibehalten. Züchtung von Sputum ergab gewöhnliches Wachstum humaner Tuberkelbazillen. Bei Züchtung von Ventrikelspülflüssigkeit am 5.7. 43 erhielt man Wachstum langer, säurefester Bazillen, die stark an Tuberkelbazillen erinnerten. Das makroskopische Aussehen der Kultur sprach indes nicht für Tuberkulose, weshalb Kulturmaterial auf zwei Meerschwein-



chen verimpft wurde. Die Meerschweinchenproben fielen negativ aus. Neue Züchtung von Ventrikelspülflüssigkeit im Juni 1944 hatte negatives Ergebnis.

Diagnose: Tbc. pulm. dxt. c. pnth. artif. dxt. Die von Ventrikelspülflüssigkeit reingezüchteten säurefesten Saprophyten waren in diesem Fall nur von beschränktem Interesse. Eine Fehldeutung derselben hätte die Behandlung nicht beeinflusst.

Fall 7. 48jähriger Mann.

Weil bei einer Tochter Tuberkulose konstatiert worden war, wurde Pat. im März 1944 untersucht, wobei man eine doppelseitige Spitzentuberkulose älteren Datums entdeckte. Diese dürfte nicht ausgeheilt sein, war aber während der Beobachtungszeit stationär. Die Tuberkulinreaktion war positiv. Bei Züchtung von Ventrikelspülflüssigkeit erhielt man Wachstum säurefester Stäbchen, die stark an Tuberkelbazillen erinnerten. Zwei mit Kulturmaterial geimpfte Meerschweinchen bekamen indes keine Tuberkulose, weshalb also die Stäbchen säurefeste Saprophyten waren.

Diagnose: Tbc. pulm. amb. inveterat. Wenn die säurefesten Stäbchen als Tuberkelbazillen gedeutet worden wären, hätte Pat. sicher unnötig Sanatoriumbehandlung erhalten.

Fall 8. 9jähriger Knabe.

Wegen Tuberkulose des Vaters stand Pat. unter Kontrolle der Zentral-lungenfürsorgestelle in Uppsala. Im Januar 1944 wurde ein kleines Infiltrat im Herz-Leber-Winkel konstatiert, welches nur langsam zurückging. Noch auf einem Film vom 28. 8. 44 ist ein kleinerer Teil dieses Infiltrats zu sehen, welches tuberkulösen Ursprung haben dürfte. Die Tuberkulinreaktion war positiv. Bei Züchtung von Ventrikelspülflüssigkeit erhielt man Wachstum säurefester, stark tuberkelbazillenartiger Stäbchen. Zwei Meerschweinchenproben mit Kulturmaterial fielen indes negativ aus.

Diagnose: Tbc. pulm. dxt.? Der Nachweis säurefester Saprophyten hat nur beschränktes Interesse. Eine Fehlbeurteilung der Bazillen hätte die Behandlung nicht geändert. Pat. wäre auch dann nur unter Kontrolle gestellt worden.

Fall 9. 22jähriger Mann.

Keine Tuberkulose in der Familie. Behandlung August—September 1941 im Garnisonskrankenhaus in Stockholm wegen rechtsseitiger Lungentuberkulose. Vom 20. 6. bis zum 27. 7. zwecks Beobachtung im Zentralsanatorium in Uppsala, wo man eine lichte Kleinfleckigkeit im rechten

Scl-I. feststellte. Im übrigen waren die Lungen ganz normal. Sputum und Züchtung von Ventrikelspülflüssigkeit negativ. Tuberkulinreaktion positiv. Stand seitdem unter Kontrolle der Zentrallungenfürsorgestelle in Uppsala. Röntgenbilder vom 12. 1. 43 und 19. 7. 44 zeigen völlig unveränderten Status. Bei Züchtung von Ventrikelspülflüssigkeit im September 1944 erhielt man Wachstum orangegelber, schmieriger Kolonien, welche säurefeste, tuberkelbazillenartige Stäbchen enthielten. Impfung von Kulturmateriel bei 2 Meerschweinchenproben hatte negatives Ergebnis.

Diagnose: Tbc. pulm. dxt. inveterat (sanat.). Eine Fehldeutung der säurefesten Saprophyten hätte Sanatoriumbehandlung und unnötige Massnahmen zwecks Verhütung von Ansteckung der Umgebung zur Folge haben können.

Fall 10. 38jähriger Mann.

Tuberkulose in der Familie. Im Januar 1936 wurde eine ziemlich unbedeutende doppelseitige Spitzentuberkulose konstatiert, die bei allen Röntgenkontrollen ein unverändertes Aussehen zeigte. Die Veränderungen waren älteren Datums, möglicherweise ausgeheilt. Sputumproben und Züchtung von Sputum gaben negatives Resultat. Im April 1944 konnten indes ziemlich reichliche »Tuberkelbazillen« bei mikroskopischer Untersuchung von Sputum nachgewiesen werden. Pat. wurde deshalb in das Zentralsanatorium in Uppsala aufgenommen und dort vom 30. 5. bis zum 22. 7. 1944 behandelt. Die Tuberkulinreaktion war positiv. Die fünf ersten Sputumproben enthielten regelmässig »Tuberkelbazillen«. Auch bei Züchtung von Sputum erhielt man Wachstum säurefester, tuberkelbazillenartiger Stäbchen. Material der Kultur wurde auf drei Meerschweinchen verimpft, von denen zwei bei der Sektion keinerlei pathologische Veränderungen zeigten, während das dritte kleine Veränderungen (örtlich vergrösserte Lymphdrüsen) aufwies, welche jedoch nicht grösser waren als solche, die nach Einspritzung säurefester Saprophyten entstehen können. Die inneren Organe, auch die Milz, waren normal. Das Sputum wurde später wieder normal. Säurefeste Stäbchen waren bei Mikroskopie nicht mehr nachweisbar.

Diagnose: Tbc. pulm. amb. inveterat. (sanata?). In diesem Fall kamen die säurefesten Saprophyten mit Sicherheit bei dem Patienten vor und waren also nicht dem Kulturmateriel bei dessen Behandlung zugeführt worden. Eine Fehldeutung lag hier ausserordentlich nahe. Hätte man nicht die Meerschweinchenpathogenität der Bazillen geprüft, so hätte Pat. wahrscheinlich noch länger im Sanatorium behandelt werden müssen, was ganz unnötig gewesen wäre.

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Wie aus dem Gesagten hervorgeht, sind säurefeste Saprophyten relativ gewöhnlich bei Züchtung von Material von kranken Menschen (bei meiner Untersuchung 0.6 %, in Lester's grosser Zusammenstellung 0.5 %. Dies muss allgemein bekannt werden, da man sonst folgenschwere Irrtümer begehen kann. Ich erinnere an die zwei früher von mir beobachteten und zu Anfang dieser Arbeit beschriebenen Fälle von Bronchiektasien. Beide waren wiederholt lange unter der unrichtigen Diagnose Lungentuberkulose im Sanatorium behandelt worden. Wie gross die Gefahr ist, dass man dabei eine vorher nicht vorhandene Krankheit bekommt, liegt auf der Hand, und die Gefahr war hier um so grösser, als die Widerstandskraft der Patienten durch Intoxikation von seiten der Bronchiektasien herabgesetzt war. Infolge meiner Kenntnis von der Existenz der säurefesten Saprophyten war ich während mehr als eines Jahrzehnts auf der Wacht vor Irrtümern. Ich pflege nämlich bei einem Patienten mit bronchiektatischen Veränderungen säurefeste Stäbchen nicht als Tuberkelbazillen anzuerkennen, bevor sie sich als meerschweinchenpathogen erwiesen haben. Ebenso wenig habe ich mich, wenn das mikroskopische Aussehen von säurefesten Bazillen oder Kulturen von solchen eine Abweichung vom Normalen zeigte, endgültig für die Diagnose Lungentuberkulose entschieden, bevor die Bazillen positive Meerschweinchenproben ergeben hatten. Auf diese Weise konnten Irrtümer vermieden werden. In vier der Fälle (Fall 1, 5, 6 und 8) spielte das Vorhandensein säurefester Saprophyten keine Rolle. Sämtliche hatten aktive Tuberkulose. Die drei ersten Fälle wurden aufgenommen und erhielten die erforderliche Pflege, der vierte (Fall 8) wurde unter Beobachtung gestellt. Eine Fehldeutung der säurefesten Saprophyten hätte die Behandlung nicht geändert. Anders verhielt es sich in Fall 10, der Lungentuberkulose hatte und 2 Monate Sanatoriumbehandlung erhielt, obgleich solche nicht notwendig war. Wären die Kulturen nicht auf ihre Pathogenität geprüft worden, so hätte man die Sanatoriumpflege sicher stark verlängert. Dieser Fall war besonders trügerisch, da tuberkelbazillenartige Stäbchen nicht bloss bei Züchtung erhalten, sondern auch in mehreren Sputumproben bei direkter mikroskopischer Untersuchung konstatiert wurden. Hier war es der Gegensatz zwischen einem plötzlich auftretenden, reichlichen Vorkommen von »Tuberkelbazillen« und dem Fehlen röntgenologischer Zeichen von Aktivität der

Lungenveränderungen (stationär seit 9 Jahren), der den Verdacht auf säurefeste Saprophyten lenkte. Die Fälle 2—4, 7 und 9 hatten sämtlich Tuberkulose älteren Datums. In manchen dieser Fälle war die Krankheit möglicherweise ausgeheilt. Die Prüfung der Meerschweinchenpathogenität der säurefesten Stäbchen, bevor man Massnahmen ergriff, hat diesen Patienten Sanatoriumbehandlung erspart.

Das makro- und mikroskopische Aussehen der Kultur ergibt sich des näheren aus Tab. 3.

Aus Tab. 3 ist ersichtlich, dass nur in Fall 10 die Kultur von säurefesten Saprophyten makroskopisch humaner Tuberkulose glich. In allen übrigen Fällen wich das Aussehen wesentlich von dieser ab, was natürlich immer den Verdacht auf Saprophyten richten muss. Statt gelbpigmentierter, trockener, undurchsichtiger Kolonien fand sich im allgemeinen ein schmieriges Wachstum oder eine zähe Haut von wechselnder Farbe: gelb, gelbbraun, gelbrost oder ziegelrot. Auch mikroskopisch variierte das Aussehen ziemlich stark. In 9 der 10 Fälle kamen nur säurefeste Stäbchen vor, die an Tuberkelbazillen erinnerten. In Fall 4 dagegen wurden auch säurefeste Kokken sowie nicht säurefeste Kokken und Stäbchen konstatiert. Die Variation der in der Kultur enthaltenen Virusformen sowie auch relativ rasches Wachstum auf dem Substrat müssen natürlich immer an säurefeste Saprophyten denken lassen, aber man darf sich nicht wundern, wenn die Meerschweinchenprobe gleichwohl in solchen Fällen gelegentlich positiv ausfällt. Ich will dies mit Beispielen belegen. Züchtung von Sputum eines 63jährigen Patienten mit zweifellosen, aber ziemlich unbedeutenden Veränderungen tuberkulöser Natur gab schon nach 19 Tagen Wachstum von säurefesten Stäbchen und Kokken sowie von nicht säurefesten Stäbchen und Kokken. Das mikroskopische Aussehen und das verhältnismässig rasche Wachstum sprachen also für säurefeste Saprophyten. Nichtsdestoweniger zeigten beide Meerschweinchen, die mit Material von der Kultur geimpft wurden, typische tuberkulöse Veränderungen. Züchtung von Ventrikelspülflüssigkeit eines 8jährigen Mädchens mit Primärtuberkulose (Tbc. lgl. bronchial. et Tbc. pulm. sin.), das noch im Zentralsanatorium gepflegt wird, ergab folgendes: Ein Röhrchen enthielt gelbe Knötchen mit säurefesten und nicht säurefesten Kokken sowie einzelnen säurefesten Stäbchen, ein anderes gelbrote Knötchen, bestehend aus

Nr.	Name	Alter	Diagnose	Sputum mikro- skopisch	Sputum- kultur	Kultur von Magen- spülflüs- sigkeit
1	M. T.	16	Pleurit. exs. + Tbc. pulm. dxt. levis	—		—
2	G. F.	33	Tbc. pulm. sin. (sanat.). Stat. post thoracoplast.	—		+
3	A. K.	48	Tbc. pulm. dxt. in- veterat. (sanata?) + Sequel. pleurit. sin.	—	+	
4	H. H.	32	Tbc. pulm. dxt. in- veterat. (sanata?)	—		+
5	T. E.	4	Tbc. lymphogland. hili sin. et mediast. (Tbc. prim.)	—		+
6	G. A.	34	Tbc. pulm. dxt.	+	+ humanes Wachstum	+
7	G. F.	48	Tbc. pulm. amb. in- veterat.	—		+
8	K. E.	9	Tbc. pulm. dxt?	—		+
9	A. J.	22	Tbc. pulm. dxt. invet. (sanata?)	—		+
10	A. H.	38	Tbc. pulm. amb. invet. (sanata?)	+	+	

Untersuchte ositive Kultur von	Das Aussehen der positiven Kultur		Meerschwein- chenprobe mit positiver Kultur
	Makroskopisch	Mikroskopisch	
Neurafflüssig- zeit	Feuchte, erst unpigmentierte, später schwach gelbe Kolo- nien	Hallberg: Nur säurefeste Stäbchen von etwas wech- selnder Länge	—
Ventrikelspül- lüssigkeit	Gelbrote, glatte, etwas feuchte Kolonien	Hallberg=Ziehl: Stark tbb- artige, säurefeste Stäbchen	—
putum	Schmieriges, schmutzgelbes Wachstum	Hallberg=Ziehl: Dicke, kurze säurefeste Stäbchen	—
entrikelspül- lüssigkeit	Röhrchen 1: Nadelspitzengros- se, etwas feuchte Kolonien in reichlicher Menge.	Röhrchen 1: Hallberg=Ziehl: Reichlich nicht säurefeste Stäbchen und Kokken, ziem- lich reichlich säurefeste Stäbchen und Kokken.	—
	Röhrchen 2: Zitronengelber, feuchter Teppich	Röhrchen 2: Hallberg=Ziehl: Teils ziemlich dicke, säure- feste Stäbchen, teils einzelne nicht säurefeste Stäbchen.	—
itrikelspül- lüssigkeit	Gelbrote, etwas feuchte Kolo- nien in einem Röhrchen. Zwei Röhrchen ohne Wachstum	Hallberg=Ziehl: Stark tbb- artige säurefeste Stäbchen	—
Ventrikelspül- lüssigkeit	Gelbrote Knötchen	Hallberg: Lange, säurefeste, stark tbb-artige Stäbchen	—
Ventrikelspül- lüssigkeit	Gelbrote, schmierige Kolonie	Hallberg=Ziehl: Säurefeste, stark tbb-artige Stäbchen	—
Ventrikelspül- lüssigkeit	Gelbrote, schmierige Kolonie	Hallberg=Ziehl: Säurefeste, stark tbb-artige Stäbchen	—
Ventrikelspül- lüssigkeit	Orangegelbe, schmierige Kolonien	Hallberg=Ziehl: Säurefeste, tbb-artige Stäbchen	—
putum	Wachstum von gleichem Aus- sehen wie humane Tuberkulose	Hallberg=Ziehl: Stark tbb- artige Stäbchen	—

zahlreichen säurefesten und spärlichen nicht säurefesten Stäbchen. Beide Röhren gaben bei Impfung positive Meerschweinchenprobe.

Hieraus kann man den Schluss ziehen, dass typisches humanes Wachstum säurefeste Saprophyten enthalten kann. Wachstum, dessen Aussehen deutlich von dem bei humaner und boviner Tuberkulose gewöhnlichen abweicht, kann gleichwohl aus Tuberkelbazillen bestehen. Dasselbe kann der Fall sein, wenn ausser säurefesten Stäbchen auch säurefeste Kokken bzw. nicht säurefeste Stäbchen oder Kokken in der Kultur vorkommen. Abweichungen im makro- bzw. mikroskopischen Aussehen des Wachstums müssen jedoch stets an säurefeste Saprophyten denken lassen. Entscheidend ist der Ausfall der Meerschweinchenproben.

Von wo stammten nun die säurefesten Saprophyten in den 10 Fällen? Tab. 3 zeigt, dass sie 7mal bei Züchtung von Ventrikel- flüssigkeit erhalten wurden, 2mal von Sputum und 1mal von Pleuraflüssigkeit. Die Ziffern sind zu klein, als dass man mit Sicherheit sagen könnte, welches Material bei Kultur am häufigsten Wachstum säurefester Saprophyten gibt. Lester fand bei einem bedeutend grösseren Material, dass dies bei Ventrikelspülflüssigkeit der Fall ist. Meine Untersuchungen deuten in dieselbe Richtung. Bei Züchtung von 726 Ventrikelspülflüssigkeiten wurden nämlich in 7 Fällen säurefeste Saprophyten erhalten, während die entsprechende Ziffer bei Kultur von 748 Sputumpräparaten nur 2 war.

Die säurefesten Saprophyten können theoretisch von dem Substrat oder von dem Patienten stammen oder dem Material bei dessen Behandlung von aussen zugeführt worden sein. In Übereinstimmung mit Lester messe ich dem Substrat in dieser Beziehung keine Bedeutung bei. Wie sich näher aus der obigen Beschreibung der Bereitung des Substrats ergibt, wurde dieses sehr sorgfältig sterilisiert und danach ausserdem auf seine Sterilität geprüft. Wenn das Substrat eine Rolle für die Entstehung säurefester Saprophyten spielen würde, müssten solche übrigens bedeutend häufiger vorgekommen sein, als es tatsächlich der Fall war, da jedesmal eine ziemlich grosse Menge Substrat hergestellt wurde. Die säurefesten Stäbchen könnten von dem Patienten stammen. Dies taten sie zweifellos in Fall 10, wo säurefeste Stäbchen in mehreren Sputumproben bei gewöhnlicher mikroskopischer Untersuchung festgestellt wurden. In Fall 3, wo Züchtung von

Sputum stattfand, und in Fall 1, wo Züchtung von Pleuraflüssigkeit vorgenommen wurde, waren dagegen bei Mikroskopie keine säurefesten Stäbchen vor der Züchtung nachweisbar. Mikroskopische Untersuchung ging der Züchtung von Ventrikelspülflüssigkeit nicht vorher. Deshalb lässt sich nichts Bestimmtes über die Herkunft der säurefesten Saprophyten in diesen Fällen sagen. Aber es ist wohlbekannt, dass säurefeste Saprophyten sowohl in der Ventrikelspülflüssigkeit als im Sputum vorkommen können. Nur in einem der 10 Fälle fanden sich also die säurefesten Saprophyten mit Sicherheit bei dem Patienten. Möglicherweise verhielt es sich in dem einen oder anderen der übrigen Fälle ebenso, doch lässt sich dies jetzt nicht beweisen. Die säurefesten Saprophyten stammten somit in gewissen Fällen von dem untersuchten Material. In andern Fällen dürften sie während der Zubereitung, die der Züchtung vorherging, von aussen gekommen sein.

### Zusammenfassung.

1. Säurefeste Saprophyten erhält man bei Züchtung von Sputum, Ventrikelspülflüssigkeit und Pleuraflüssigkeit bedeutend häufiger, als man im allgemeinen annimmt. Bei dieser Untersuchung wurden solche in 10 von 1654 Kulturen nachgewiesen, d.h. in ungefähr 0.6 %.

2. Säurefeste Saprophyten und Tuberkelbazillen können sowohl in Kultur als unter dem Mikroskop dasselbe Aussehen haben. Eine Kultur, die aus Tuberkelbazillen zu bestehen scheint, kann säurefeste Saprophyten enthalten. Andererseits kann gelegentlich eine Kultur, die ein von Tuberkulose abweichendes Aussehen hat, dennoch Tuberkelbazillen enthalten.

3. Säurefeste Saprophyten sind eine gefährliche Fehlerquelle bei Züchtung. Welche Irrtümer begangen werden können, zeigt der Bericht über 2 früher und 10 in letzter Zeit nachgewiesene Fälle, wo Saprophyten bei Züchtung erhalten wurden.

4. Für säurefeste Saprophyten spricht ein von Tuberkulose abweichendes makro- und mikroskopisches Aussehen (gleichzeitiges Vorkommen von säurefesten Stäbchen und Kokken bzw. nicht säurefesten Stäbchen und Kokken). Dasselbe gilt, wenn die Kultur rascher wächst, als es bei Tuberkulose gewöhnlich ist. Sicher



kann man dessen indes nicht sein, wie aus zwei angeführten Beispielen hervorgeht.

5. Fehldiagnostik kann in folgender Weise vermieden werden: An Orten, wo Meerschweinchenproben ohne grössere Kosten ausführbar sind oder Untersuchung des Bakterienvorkommens in Sputum, Ventrikelspülflüssigkeit usw. nur selten in Frage kommt, sollte nicht Züchtung, sondern nur Meerschweinchenprobe stattfinden. Wenn Bakterienuntersuchung in grösserem Umfang vorgenommen wird und man also aus wirtschaftlichen Gründen auf die zuverlässigere Meerschweinchenprobe verzichten muss, ist Züchtung die gegebene Methode. Um Verwechslung mit säurefesten Saprophyten zu vermeiden, ist jedoch eine ergänzende Meerschweinchenprobe unter folgenden Voraussetzungen auszuführen:

a) Wenn der Nachweis säurefester Stäbchen bei Kultur oder bei direkter mikroskopischer Untersuchung dem klinischen Bilde widerspricht,

b) wenn säurefeste Stäbchen bei Bronchiektasiepatienten nachgewiesen werden,

c) wenn die erhaltene Kultur säurefester Stäbchen makro- oder mikroskopisch von gewöhnlichem humanem oder bovinem Wachstum abweicht.

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From the Neurologic Clinic of the Serafim Hospital, Stockholm. (Chief:  
Professor Nils Antoni)

## Polyneuritis following Sulfanilamide Therapy.

By

RAGNAR MÜLLER.

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It is well known that the therapeutic use of sulfanilamide or any related drug involves certain risks. More or less severe complications may arise due to disturbances of different organs or organic systems. Among the severe concurrent diseases due to involvement of the nervous system, polyneuritis is of most common occurrence.

The experiments of Bieler and coworkers on animals have demonstrated that all sulfanilamide compounds may produce organic alterations of the nervous system. The administration of sulfamethylthiazole, sulfanilyldimethylsulfanilamide (uliron) and sulfafenylthiazole produces extensive and marked alterations, whereas after the use of sulfanilamide, sulfapyridine and sulfathiazole only mild and inconstant alterations are liable to occur. Clinical experience also indicates that the nervous system is especially susceptible to the action of sulfanilamide compounds substituted with methyl. Thus, polyneuritis was almost exclusively observed after uliron and sulfamethylthiazole therapy, although these preparations are considerably less extensively used as therapeutic agents than other sulfanilamide compounds. Nyman stated that the sulfanilamide compounds in this respect are comparable to certain alkaloids such as strychnine, morphine, cocaine, veratrine and atropine which also show increased affinity to the nervous system if methyl is added.

As early as 1940, Plügge collected from the literature 70 cases of uliron polyneuritis. About 20 cases of sulfamethylthiazole polyneuritis are described in the medical literature.<sup>1</sup> The majority of these were published in the Danish literature to which Bruun and Hermann (1942) contributed with 10 cases and Østgaard (1942) with 3. In the Swiss literature 2 cases were published by Gsell, and in the American literature Brown and Herell reported 3 cases. Only a few cases of polyneuritis as a result of the administration of other sulfanilamide compounds are known<sup>1</sup> and may be classified as follows: 4 cases after sulfanilamide (Ornsteen and Furst, 1938, Alder and Machoff, 1938, Bruun and Hermann, 1942), 3 cases after sulfapyridine (Plügge, 1940, Petrén, 1941, Sugar, 1942), 1 case after sulfapyridine (Little, 1942), 5 cases after sulfathiazole (Pedersen, 1942, Bruun and Hermann, 1942, Little, 1942).

During the last four years 7 patients manifesting polyneuritis as a result of chemotherapy were treated at the Neurologic Clinic of the Serafim Hospital, Stockholm. The present material includes 1 case of uliron polyneuritis that was previously described by K. A. Ekbom, and 1 case to which sulfapyridine and sulfathiazole were administered in addition to uliron. In the remaining 5 cases polyneuritis occurred after the use of sulfanilamide compounds which had not been substituted with methyl. Sulfanilamide was given to 1 patient, sulfathiazole to 2, and 1 patient was treated with sulfanilamide, sulfapyridine and sulfathiazole. Another patient who was treated for polyneuritis on two separate occasions was given sulfapyridine on the first occasion and sulfathiazole on the second.

*Case 1*, Female, aged 56 years, record No. 171/40 and 4/43. Since her 34th year the patient had been suffering from asthma, but otherwise enjoyed good health. In the beginning of December of the year 1939, she came into hospital because of acute pneumonia and was treated with sulfapyridine for a short period. She was given altogether 16.5 g of this drug on three separate occasions. About the end of December the patient developed violent pains in her left arm which gradually grew weak. At the end of the following week similar symptoms set in, in her right arm and were accompanied with paraesthesia and paresis in the legs. The paresis progressed to the point that at the end of a month the patient was incapable of eating or standing without assistance.

The examination of the patient at the Neurologic Clinic on March 27, 1940, showed that the muscular motility in the extremities was poor. In the left hand the active motility was absent. Her legs would not support

<sup>1</sup> The author studied the literature up to June 1, 1944.

her. The muscles of the four extremities were highly atrophic. The electric examination of the muscles revealed total reaction of degeneration in the hands and partial reaction of degeneration in the legs. She complained of violent pains in the extremities. Superficial sensibility for all qualities was diminished in the feet, lower legs, hands and forearms. Deep sensibility was diminished in the fingers and toes, especially on the right side. Not one of the muscular reflexes could be evoked in the arms. The quadriceps reflexes and the ankle reflexes did not show any abnormalities. There were no other symptoms of nervous disturbances. Examination of the cerebro-spinal fluid and of the blood did not reveal anything abnormal. The histamine test yielded 20 ml gastric juice during 45 minutes: free HCl max. 32. Ta. max. 70.

The patient was given aneurin and hepaforte for five months. As a result of this treatment there was considerable amelioration of her condition. She was discharged from the hospital relieved from pain. During her hospitalization at the Neurologic Clinic she was operated on for polypi in both nasal cavities.

The condition of the patient continued to improve after her return home. Gradually she was able to walk fairly freely, though with pronounced steppage gait. She was also partly relieved from the paresis in the upper extremities, though full extension of the fingers of the right hand was not possible and her left hand remained paralytic.

In August 1942, the patient developed a fever due to an infected excema for which she was hospitalized from Sept. 18 to Nov. 11. From Sept. 22 to Sept. 26, she was given sulfathiazole, altogether 26 g. On Nov. 14, the patient again complained of violent pains in the extremities. Six days later she manifested paraesthesia in the feet and paresis in the arms and legs. The paresis rapidly became worse until at the end of a few weeks the patient was incapable of standing without assistance and of using her left arm. On Sept. 19, the blood counts yielded 11,400 white blood cells, eosinophils 3 per cent, on Sept. 25, 17,600 white blood cells, eosinophils 12 per cent, and on Nov. 4, 30,000 white blood cells, eosinophils 66 per cent.

On Jan. 5, 1943, the examination of the patient at the Neurologic Clinic showed that her general condition was very poor. In addition to the paresis of the m. rectus int. oc. sin. she manifested extensive paresis of the muscles of all extremities. Active motility of the toes, ankles and the left hand was absent. She was incapable of standing or eating without assistance. The muscles of all extremities were highly atrophic. The electric examination revealed absence of response to stimuli in the left hand, and total reaction of degeneration of the muscles of the legs, the forearms and the right hand. The patient complained of violent pains in her legs and arms, and manifested tenderness to pressure in the muscles of the extremities, especially in the calves. Superficial sensibility for all qualities was diminished in the hands, forearms, feet and lower legs. Deep sensibility was diminished in the fingers and toes. The biceps and quadriceps reflexes could not be evoked; the other muscular reflexes were weak, even indefinite. The plantar reflexes were absent. Otherwise there were no symptoms of nervous disturbances.

During her five and a half months' stay at the Neurologic Clinic the patient was treated with aneurin. This treatment resulted in an considerable improvement of her condition. The pains subsided, and there was partial regression of the sensory disturbances, but with the exception of the paresis of the ocular muscle which completely regressed, the paresis remained unchanged.

During her hospitalization the patient periodically suffered from rather severe attacks of asthma, and on a few occasions manifested urticaria and Quinke's edema. During the last month of her stay at the hospital she developed hydrops of the knee joints on both sides. Afebrile temperature alternated with subfebrile temperature, with a few peaks of and above 39° C.

The sedimentation rate which was 18 millimeters per hour when the patient was admitted to the hospital, gradually accelerated and was 118 millimeters per hour when she left the hospital. Gradually a mild hypochronic anemia developed, in the course of which the blood counts revealed: Hemoglobin content 65 per cent, red blood cells 3,830,000. The white blood cells varied between 9,300 and 18,200. During the first month of her stay at the Neurologic Clinic the patient exhibited only a mild eosinophilia with 7 to 8 per cent eosinophils. This rapidly developed a severe character and the repeated blood counts revealed that the eosinophils varied between 30 and 55 per cent. Immature cells were not detected. In the sputum 30 per cent eosinophils were found. The feces did not contain any vermis eggs. The allergic test (including testing of the reaction to sulfathiazole) by means of the cutaneous test (Juhlin-Dannfelt) yielded negative results. The histamine test, yielded 60 ml gastric juice per 1 hour, free HCl max. 55. Ta. max. 65. The skin and the inner structures showed no abnormalities.

A few months after her discharge from the hospital the patient died. A post mortem was not made.

*Case 2.* Male, aged 19 years, record No 222/40. (This case was previously published by K. A. Ekbom). The patient who had previously enjoyed good health contracted a sore throat and a cold in the nose in the middle of February of the year 1940. A week later there was discharge from the urethra and urination was painful. He was given a total of 24 g of uliron during sixteen days. On March 10, on the twelfth day of the treatment, the patient experienced for a few hours paresthesia in the feet. On the next day he developed pains in the calves. At the end of a week the pains subsided, but weakness of the ankles and toes became manifest. The paresis impaired during the subsequent days, but then remained stationary. No signs suggesting involvement of the arms were observed. One week after the first course of uliron therapy, the patient was given a further 4.5 g of uliron, as there still was urethral discharge.

On April 23, the examination of the patient at the Neurologic Clinic showed that both big toes were paralytic and that the motility of the lateral toes was weak. The ankles flexed weakly to 120°. All other movements of these joints were likewise made with reduced strength. The patient was

incapable of standing on his toes or his heels. The paresis was somewhat more pronounced on the left side. The knee and hip joints moved fully and powerfully. Atrophic changes were not definitely recognizable. The electric examination revealed total reaction of degeneration of the m. tibialis ant. sin. and of the extensor brevis of the toes on both sides, partial reaction of degeneration of the peronei and of the gastrocnemias on both sides and of the m. tibialis ant. dx. The ankle reflex on the left side was sluggish, whereas on the right side it was normal. The quadriceps reflexes were somewhat more accentuated. The plantar reflexes could not be evoked. Otherwise there were no signs of nervous disturbances. The cerebro-spinal fluid was normal. Ewald's test meal revealed nothing abnormal.

Although the patient was given large quantities of vitamin B, he had not fully recovered at the end of one year. He still manifested a mild paresis on dorsal flexion of the left ankle.

*Case 3.* Male, aged 47 years, record No 277/40. In 1929 the patient was hospitalized for two months at the Medical Clinic of the Serafim Hospital because of polyneuritis of unknown etiology. Since then the patient noticed at times a slight numbness and tenderness to pressure in both legs following physical exertion, but otherwise was healthy. In the middle of February, the patient fell ill with angina tonsillaris. On this occasion he was given 7.5 g of sulfanilamide for a couple of days. On the second day of the treatment the patient complained of tenderness of the finger tips and of numbness in the legs. Subsequently, pains, paraesthesia and paresis developed in all extremities. The paresis gradually became worse. The condition of the patient remained stationary from the beginning of April.

On May 25, 1940, the examination of the patient at the Neurologic Clinic revealed that the legs were paralytic, and that there was but inconsiderable motility of the arms. The fingers moved inconsiderably and weakly. On forcible breathing paresis of the respiratory muscles was noticeable. The muscles of the extremities were moderately atrophic. The electric examination of the muscles did not furnish any definite evidence of abnormalities. The patient complained of moderate pains and paresthesia in the extremities. There was hypaesthesia for all qualities in the extremities. Deep sensibility was absent in the toes and diminished in the fingers. The muscular and plantar reflexes could not be evoked. Otherwise there were no symptoms of nervous disturbances. The patient manifested achylia which was refractory to histamine. The blood picture was normal.

For six weeks the patient was treated with vitamin B and heparforte. His condition improved. When he signed his release from the hospital, he could walk, though he required assistance, and move his arm with satisfactory strength. The sensory disturbances had considerably improved and the patient was relieved from pain.

*Case 4.* Male, aged 36 years, record No 818/43. The patient stated that he had been in good health until April 3, 1943, when he contracted acute pneumonia. He was treated with sulfathiazole and was given 34 g in the

course of seven days. A month later violent pains in the arms set in, associated with mild paresis. These symptoms gradually increased and at the end of a fortnight the patient had great difficulty in lifting his arms. At that stage of the disease the patient was also troubled with paraesthesia in the hands. From the end of June on, his condition remained stationary. He did not manifest any symptoms of involvement of the legs.

On Aug. 2, the examination of the patient at the Neurologic Clinic showed that he could not lift his arms higher than 45 degrees. Motility of the elbow joints was weak. He could not extend his hands which hang limply at his side. The pressure of his hand lacked strength. There was pronounced atrophy of the muscles of the upper extremities. The electric examination revealed that the atrophic muscles presented partial reaction of degeneration. There were no symptoms of paresis in the lower extremities. The patient complained of moderate pains and paraesthesia in the arms and hands. Superficial sensibility was absent in the arms and radially also in the hands. The muscular reflexes in the arms could not be evoked. The muscular reflexes in the left leg were weak, whereas in the right leg they were normal. Otherwise, there were no symptoms of nervous disturbances.

The patient did not manifest anemia, but a mild leukopenia was present. The blood examination revealed eosinophilia with 10 per cent eosinophils. The insulin test yielded 50 ml gastric juice during 1 hour, free HCl max. 9, Ta. max. 27.

For one month the patient was treated with vitamin B and insulin. The dosage of the latter was gradually increased until he manifested subcoma.

When the patient left the hospital he was relieved from pain and was no longer troubled with paraesthesia; the paresis had also slightly regressed.

*Case 5.* A girl, aged 3 years, record No 1227/43. The patient had been healthy until June 10, 1943, when she developed scarlatina. Six days subsequent to the onset of the disease she manifested symptoms of otitis media in the left ear. On June 28, trephination was performed for mastoiditis on the left side. Gradually she manifested symptoms referable to involvement of the cerebellum. On Aug. 16, she was operated on and an abscess was found localized to the left hemisphere of the cerebellum. Subsequent to the operation the patient was given from Aug. 21 to Sept. 25, sulfathiazole, 10.5 g per os and 9 g per rectum, sulfanilamide, 10.5 g per os, sulfapyridine, 3 g per os and 21.3 g intramuscularly. During the course of the chemotherapy the condition of the patient improved. Her temperature became normal, secretion from the area operated on ceased, and there was complete recovery from the cerebellar abscess. In connection with the intramuscular injections of sulfapyridine local necrotic patches developed situated in the gluteal regions and proximally in the thighs. On Sept. 14, when the necrotic patches had almost disappeared, it became apparent that the patient could not move her left leg. The left leg was almost paralytic and the strength of the right leg was also reduced. The electric examination revealed total reaction of degeneration of the extensors

of the left lower leg and partial reaction of degeneration of the extensors of the right lower leg. On Sept. 22, examination of the blood revealed 12,000 white blood cells, eosinophils 3 per cent, on Oct. 15, 11,100 white blood cells, eosinophils 7 ½ per cent, on Dec. 23, 7,600 white blood cells, eosinophils 13 ½ per cent.

The examination of the patient at the Neurologic Clinic on Nov. 9, 1943, revealed that there was absence of active motility of the left knee and ankle. She could move her left hip joint only slightly and the movements lacked strength. The toes of the left foot moved but inconsiderably. The strength of the right leg was slightly reduced. There was moderate atrophy of the muscles of the left leg. Sensibility (only pain appreciation was tested) seemed to be intact. There was absence of all muscular reflexes in the left leg, and the quadriceps reflex in the right leg could not be evoked. All other muscular reflexes and the plantar reflexes were normal. Apart from choked disks, the condition of which had not changed since the time previous to the brain operation, there were no nervous disturbances.

There was no anemia. The blood examination revealed 8,200 white blood cells, eosinophils 15 per cent. The administration of large quantities of vitamin B over a period of two months, did but inconsiderably improve the condition of the patient.

*Case 6.* Male, aged 56 years, record No 82/44. The patient had been healthy until Oct. 22, 1942, when the little finger of his left hand was struck by a hammer. A few weeks later he developed fever and a chill. From Nov. 10, 1942, until Jan. 22, 1943, he was hospitalized and treated on the diagnosis of complicated fracture of the second phalanx of the little finger of the left hand and sepsis. From Nov. 10 to Dec. 7, 1942, he was given 140 g of sulfathiazole. In the middle of December, the patient began to complain of pains in the extremities, and in the beginning of January of the year 1943, when he was allowed to get up, his legs were weak and he had difficulty in walking. The muscles of the lower legs were atrophic and the ankle reflexes could not be evoked. No information was available as to the condition of the upper extremities at that time. The examination of the patient in July revealed atrophy of the muscles of the hands and that the pressure of his hands lacked strength.

On Jan. 20, 1944, the examination at the Neurologic Clinic showed that the general condition of the patient was poor. There was obvious oligophrenia and he considerably exaggerated his condition (insurance case). The movement of the toes was greatly restricted and weak. Active motility of the ankles was absent. Motility of the knee and hip joints was powerful. The hands were weak and the wrists also lacked strength. There was no definite evidence of reduced strength of the elbow and shoulder joints. The muscles of the lower legs were highly atrophic, those of the forearms and hands only moderately so. The electric examination revealed total reaction of degeneration of the muscles of the lower legs. The ankle reflexes could not be evoked. The other muscular reflexes were normal. The plantar reflexes could not be elicited. Sensibility could not be



tested as the patient gave conflicting information. Otherwise, no symptoms of nervous disturbances were observed.

There was no anemia. The blood examination revealed 8,400 white blood cells, eosinophils 7 per cent. There was achylia which was refractory to histamine. For one month the patient was treated with vitamin B without any result.

*Case 7.* Male, aged 27 years, record No 438/44. Until Jan. 5, 1944, when the patient contracted gonorrhea, he had been in good health. Without consulting a physician, the patient took 14 g of sulfapyridine over a period of four days. Later, when he went to see a physician he was ordered to take 50 g of sulfathiazole. This drug had no effect and therefore he took a further 60 g of uliron of his own accord. In the middle of February, the patient noticed a slight tenderness of the calves and pains when walking, and a few days later, when getting up in the morning, his legs felt weak. He discontinued the uliron treatment. He was able to carry on his work as a mechanic until the middle of March when weakness in the right hand developed, and a few days later in the left one also. From then on, his condition remained stationary.

On April 17, 1944, when he was examined at the Neurologic Clinic, the pressure of both hands lacked strength. He could not abduct or adduct the fingers of the right hand, and these movements were made with reduced strength in the left hand. The thumbs could not be fully opposed. With the right ankle the patient could only make inconsiderable and weak movements, whereas the motility of the left ankle was not quite so weak. The movement in the toes was inconsiderable. The patient could not stand on his toes or heels. General strength of the wrist, elbow, shoulder, knee and thigh joints was powerful. All the muscles of the left hand were atrophic; in the right hand there was only atrophy of the muscles of the thumb. In the lower legs there was atrophy of both the flexors and extensors, especially on the right side. Superficial sensibility was slightly reduced in the feet. Deep sensibility showed no abnormalities. The brachioradialis reflexes were weak, the triceps reflex could not be evoked on the right side. The other muscular reflexes in the arms were normal. The ankle reflexes were absent. The quadriceps reflex on the right side was weak, whereas on the left side it was normal. The plantar reflexes could not be elicited. Otherwise, there were no signs of nervous disturbances.

The blood picture was normal. The histamine test did not reveal anything pathologic.

At the end of a fortnight, the patient left the hospital without showing any amelioration.

The clinical picture of polyneuritis following uliron and sulfamethylthiazole treatment is well known from the publications in the literature. The cases of uliron polyneuritis included in the present material are characteristic of the disease. Signs of motor disturbances predominate in the shape of symmetrical distal paresis which is frequ-

ently associated with marked muscular atrophy. At an early stage of the disease paresthesia and pains are of common occurrence, though not especially troublesome to the patient, and in the majority of the cases these symptoms rapidly regress. The pain is chiefly experienced as a cramp in the calves. Frequently, there is tenderness of the muscles of the affected areas. Signs of sensory deficiency are often completely absent, and, if present at all, they are comparatively slight. A characteristic of the condition is that the lower extremities are affected to a much larger extent than the upper ones. In many cases the arms are not involved at all, whereas only exceptionally are the legs not affected. Bruun-Pedersen and Dalsgaard-Nielsen described a case of polyneuritis following uliron treatment in which only the arms were affected. As a rule, the four extremities are affected, though the arms to a lesser degree than the legs.

From the study of the small number of published cases of polyneuritis occurring after the administration of non-methylated sulfanilamide compounds, it may be assumed that the clinical picture of cases of that kind is generally somewhat different. The paresis is more extensive and predilection for the distal parts of the extremities is not so pronounced. In four of the reported cases (cases 1, 3, 4, and 5), the paresis in the proximal part of the extremities was almost as severe as in the distal ones, and only in case 6 were the muscles of the proximal parts fairly intact. Polyneuritis of this kind is also more painful. Three of the patients (cases 3, 4 and 6) gave a history of violent pains of many weeks' duration. Two cases (cases 3 and 4) complained of troublesome paraesthesia. The signs of sensory deficiency were also more pronounced. Case 4 manifested an almost complete anesthesia in the arms and in cases 1 and 3 there was also pronounced hypesthesia in the extremities. In the two last-mentioned cases deep sensibility was considerably diminished in the fingers and toes. The upper and lower extremities appeared to be affected to about the same degree in most of the cases. In case 4, however, the legs were intact, though the muscular reflexes in the left leg were somewhat weaker. Even in case 1 the arms were affected to a higher degree than the legs.

To summarize, it may be stated that in cases of polyneuritis as a result of sulfanilamide, sulafapyridine and sulfathiazole, the symptoms, as a rule, are more extensive and more pronounced than

in cases of polyneuritis due to uliron and sulfamethylthiazole. Further, the clinical picture is not to the same extent marked by predominance of signs of motor disturbances as in polyneuritis following uliron and sulfamethylthiazole.

Signs from the cranial nerves are very rarely manifested. Van Valkenburg and von dem Borne described a case of uliron polyneuritis which was associated with anosmia, ageusia, pharyngeal paresis and sensory disturbances in the face. Bucy reported a case of optic neuritis due to uliron. One of the patients reported here, (case 1), developed paresis of one of the ocular muscles after sulfathiazole treatment. Case 3 exhibited a mild paresis of the respiratory muscles, a symptom which, as far as the author knows, has previously not been reported as concurrent with polyneuritis of this kind.

In certain cases symptoms of polyneuritis even set in during the course of the treatment, whereas the majority of the cases did not manifest the first symptoms until several days or weeks after the treatment had been discontinued. According to Hüllstrung and Krause »incubation time», as a rule, covers a period of twenty days. In the present material »incubation» took, eighteen, thirty, nineteen and eight days respectively. Of the four patients who showed symptoms of the onset of the disease during the course of the treatment, three did not manifest these symptoms before the twelfth day of the treatment. In case 3 there was manifestation of symptoms as early as the second day of the treatment. This, however, was due to certain conditions which will be referred to later on in this paper.

Nothing definite can as yet be said about the duration of the disease, and the possibilities of cure, because the follow-up time has been too short in the majority of the cases published so far. As a rule, however, the symptoms are still manifested at the end of three to five months. The prospect of recovery does not seem to be very favourable, an assumption which, among other things, is supported by the fact that the electric examination of the muscles frequently reveals total reaction of degeneration of the affected muscles. One of the reported cases, case 1, after two years and six months was still manifesting paresis and contracture in one hand and paresis of the peroneus in both sides. The other patients described in the present paper also exhibited severe disturbances causing invalidity even after a follow-up period of from two and

Case	Sex and Age	Indication	Drug and Total Dosis	Treatment Time	Onset	Duration
1	Female, 56 years	Acute Pneumonia	Sulfapyridine 16.5 g	3 courses during about a fortnight.	Towards the end of the treatment	2 1/2 years
			Sulfathiazole 26 g	4 days	On the eighteenth day after discontinuance of the treatment	> 6 months
2	Male, 19	Gonorrhea,	Uliron 24 g	16 "	On the twelfth day of the treatment	> 1 year
3	Male, 47	Angina tons.	Sulfanilamide 7.5 g	3 "	On the second day of the treatment.	> 5 months
4	Male, 36	Acute Pneumonia	Sulfathiazole 34 g	7 "	One month after discontinuance of the treatment.	> 4 months
5	Girl, 3	Abscess. cerebelli.	Sulfathiazole 15 g Sulfanilamide 10.5 g Sulfapyridine 24.3 g	Several courses during 1 month	On the nineteenth day after discontinuance of the treatment.	> 3 months
6	Male, 56	Sepsis	Sulfathiazole 140 g	1 month	On the eighth day after discontinuance of the treatment.	> 1 year and 2 months
7	Male, 27	Gonorrhea	Sulfapyridine 14 g Sulfathiazole 50 g Uliron 62 g	Several courses during 1 month	Towards the end of the treatment.	> 2 and a half months

of half months to one year. Polyneuritis due to sulfanilamide should therefore be considered as a very severe complication which, as a rule, keeps the patient from work for months, and sometimes even disables him for life. Compared with the prospect of recovery in cases of polyneuritis due to other causative agents, the prognosis for sulfanilamide polyneuritis seems to be unfavourable, though no lethal exit from this kind of polyneuritis has so far been reported.

Chemotherapy in cases of polyneuritis of this kind, has, without any doubt, an important bearing on its development. It might, of course, be possible that the primary disease which is an infectious one, gives rise to polyneuritis in these cases. On the other hand, however, this assumption hardly holds good in view of the fact that polyneuritis hardly ever or only very rarely coexists with such infectious diseases as gonorrhea and pneumonia. Nevertheless the possibility should not be excluded of infectious diseases having some, though minor bearing on the origin of polyneuritis, as is frequently the case in polyneuritis due to alcoholism.

Sulfanilamide and related drugs might produce polyneuritis by a direct toxic action on the nerve tissues or by sensibilization.

If the disease is assumed to be due to a toxic action of the drugs, then one is inclined to suppose that the quantities which are administered to the patient have a decisive bearing on its development. In some of the cases published in the literature, large quantities of sulfanilamide preparations certainly had been administered. As a rule, however, the total dose did not exceed 20 to 40 g which may be called a moderate dose, and in some cases polyneuritis even occurred after the administration of very weak doses. In one of the cases published by Bruun and Hermann the patient had not been given more than 7.2 g of sulfanilamide. The Tables included in this paper, show the total dosage given to the reported cases. As may be seen, the total dose, at least in cases 1 and 3 was very weak. No correlation between the strength of the dose administered to the patient and the degree of the severity of polyneuritis is demonstrable, though such should exist, if a toxic action of the drug is taken for granted. In this connection it should be realized that concentration of sulfanilamide and its compounds in the blood and tissues does not depend exclusively on dosage, but also on renal discharge. If this is diminished a toxic damage may occur, even if small quantities of sulfanilamide or of any related drug

are administered. The assumption that patients suffering from polyneuritis exhibit kidney troubles to a larger extent than other individuals, is not justified, however, as in many of these cases the patients who were treated, say for gonorrhea, were young people who had previously been healthy (Eruun and Hern ann). It is therefore, hardly probable that polyneuritis following sulfanilamide therapy is, as a rule, due to the toxicity of this drug to the nerve tissues.

Allergic manifestations such as pyrexia, chills and exanthema after the therapeutic use of sulfanilamide are well known. Many circumstances support the assumption that polyneuritis also may be the manifestation of an allergic reaction. Polyneuritis, like drug fever and exanthema, occurs strikingly often after the intermittent administration of sulfanilamide or any related drug (this was the case in three of the reported cases) as well as in the cases which had undergone chemotherapy on a previous occasion. On uninterrupted treatment, the allergic symptom, as a rule, are not recognizable before the eighth or ninth day of the treatment, a fact which is also observed as regards the onset of symptoms in polyneuritis. The assumption of an allergic genesis of the disease is further supported by the fact that the quantity of the drug administered does not seem to be significant. It is rather interesting to note that four of the reported patients manifested blood eosinophilia, a condition which, as a rule, only occurs in the presence of allergic polyneuritis (disturbances due to the administration of serum, periarteritis nodosa). In two instances, cases 1 and 3, blood eosinophilia occurred in conjunction with the onset of the first symptoms of polyneuritis. In this connection case 1 is especially interesting. It is the case of a woman aged 59 years who since her 34th year had been suffering from asthma. In 1940 she was treated for pneumonia with sulfa-pyridine. During the course of this treatment she contracted polyneuritis. Two years later, on the occasion of a therapy with sulfathiazole, polyneuritis recurred accompanied by severe blood eosinophilia with 66 per cent eosinophils. Four months later, when she was admitted to the Neurologic Clinic, her general condition was very poor and she manifested severe polyneuritis. During her stay at the hospital the patient had at times rather severe attacks of asthma and manifested urticaria and Quinke's edema during short periods. Afebrile temperature alternated with subfebrile temperature and the sedimentation rate was grossly accelerated. Repeated

blood counts revealed a moderate leukocytosis and eosinophils up to 50 per cent. At the end of a treatment of five and a half months' duration the patient was discharged from the hospital and died shortly after her return home. No post mortem was made. Rankeman (1939), stated that the coexistence of asthma, polyneuritis and blood eosinophilia is characteristic of periarthritis nodosa. In addition to the eight cases which came under the personal observation of this author and of which seven were verified at the post-mortem examination, he published further nineteen cases which he had collected from the literature. Svanberg recently described a case of periarthritis nodosa exhibiting this symptom complex. The picture of the disease in case 1 is so characteristic that it was assumed to warrant the diagnosis of periarthritis nodosa, in spite of the fact that the condition was histologically not verified.

Contrary to the previous conception that periarthritis nodosa is a disease in itself, it is nowadays considered to be a syndrome indicative of allergic reactions, produced by different antigens. In case 1 of the present material it may be assumed that the sulfanilamide preparation played the part of an antigen.

Sensibilization for sulfanilamide and related drugs is comparable to the sensibilization produced by albumin. Polyneuritis is also apt to occur after serum treatment.

Polyneuritis is very rarely concurrent with chemotherapy. On the basis of the study of a comprehensive material Frisk reported a frequency of only 0.1 to 0.2 per cent. It may, therefore, be assumed that a certain predisposition of the individual for this disease or some special causative agent have a decisive bearing on the origin of polyneuritis.

It is obvious that a nervous system manifesting lesions due to some previous damage is especially susceptible to chemotherapy, a fact which was observed by several authors. Bruun and Hermann described three cases which contracted mononeuritis within an area which previously had been damaged due to some mechanical or infectious action. One of the cases reported here also illustrates the reduced resistance of nerve tissues which had previously been damaged. This is the case of a man aged 47 years (case 3) in whom the administration of only 7.5 g of sulfanilamide resulted in the recurrence of polyneuritis from which he had suffered ten years previously and the origin of which was obscure.

The fact that the nervous system is more susceptible to damage in the presence of achylia, has been well known for a long time. In this connection the so-called gastrogenic myelopathy and the common coexistence of achylia with the different types of polyneuritis should be recalled. This fact, however, has so far not been viewed from this angle when discussing the pathogenesis of polyneuritis due to sulfanilamide. In six of the reported cases the gastric juice was examined. The test meal revealed normal conditions in two cases only. Two patients manifested achylia which was refractory to histamine, in one patient there was pronounced hyposecretion and the histamine test revealed reduced acidity values, and a further patient on whom the insulin test was made, showed almost absolute achylia. Hüllstrung, having demonstrated that sulfanilamide and its compounds have no action on the secretion of gastric juice, the deficiency in the secretion of gastric juice recognized in the cases described here cannot be explained by the action of chemotherapy. Deficient secretion of gastric juice most likely predisposes the patient to polyneuritis due to chemotherapy.

Whether insufficiency of vitamin B<sub>1</sub> is present in polyneuritis of this kind is still disputed. Engelhardt and Hüllstrung found that if aneurin was administered parenterally to pigeons, it had both a prophylactic and a therapeutic effect on paresis due to uliron. According to this author, this paresis might be due to a deficiency in aneurin. Van Valkenburg and von dem Borne also expressed the view that deficiency in vitamin B<sub>1</sub> was of major pathogenetic importance to polyneuritis due to sulfanilamide. Other authors, however, (Bruun and Hermann) stated that neither the past history nor the condition of the patient furnished any information as to the presence of deficiency in aneurin in cases of this type, a fact which concurs with the experience on the cases treated at the Neurologic Clinic. In view of the fact that the therapeutic use of aneurin on man yielded hardly any results, it does not seem likely that deficiency in aneurin is of common occurrence in the presence of polyneuritis of this kind. It is possible, however, that if there is deficiency of aneurin, the nervous system is more susceptible to the action of sulfanilamide or any of its compounds than under normal conditions.

Engelhardt and coworkers unvaryingly produced paresis in pigeons fed with small quantities of uliron and disceptal if the ani-



imals were exposed to powerful muscular exertion simultaneously with the administration of the drug, or shortly afterwards. If the animals were given strenuous muscular exercise immediately after the ingestion of uliron or diseptal, the paresis was even more pronounced and smaller quantities of the drug were required. Animals which were not given any exercise, manifested paresis on exceptional occasions only, even if they were fed on larger quantities of uliron or diseptal than had been given in the previous experiment. It was also observed on man that polyneuritis due to sulfanilamide and any related drug frequently became manifest after physical exertion. Leroy published a case of polyneuritis due to uliron in which the disease set in after the patient had taken an exceptionally long walk, and Tietze reported the case of a soldier who manifested polyneuritis subsequent to a parade march. One of the patients (case 7) developed pains and paresis in the legs in the course of uliron treatment. He discontinued the treatment, and was able to carry on his work which, as he was a mechanic, was a great strain on his hands, until he manifested severe paresis in both hands and which set in about a month later. As previously mentioned the first symptoms frequently occurred subsequent to a course of chemotherapy, and in many cases subsequent to muscular exercise while the patient was up for the first time after a prolonged rest in bed (Brunn and Hermann). Many observations support the assumption that in the presence of polyneuritis due to sulfanilamide or any related drug, muscular exercise may give rise to symptoms as is the case in polyneuritis due to other causative agents. Muscular exertion increases the functional strain on the nerves, a fact which may cause a latent insufficiency to become manifest.

On the basis of the discussion on the pathogenesis of polyneuritis due to sulfanilamide or any of its compounds, the following conclusions may be drawn: The possibility cannot be excluded that in certain cases polyneuritis occurs as a result of a purely toxic damage to the nerve tissue. As a rule, however, it seems to be due to sensibilization, as it happens in polyneuritis occurring after the therapeutic use of serum. Previous damage to the nervous system, deficient secretion of gastric juice and deficiency in aneurin are factors predisposing to this disease. Muscular exercise may cause a latent polyneuritis to become manifest.

In order to avoid as far as possible the development of poly-

neuritis, certain principles should be observed when administering sulfanilamide or any related drug. Judicious administration of sulfanilamide or any of its compounds is of major importance. The patient should be given chemotherapy only on condition that this treatment is definitely indicated. If this is the case, then all established rules should be strictly followed. The drug should be administered during as short a period as possible; intermittent administration should be avoided. Preparations substituted with methyl should not be administered. Such patients as manifested symptoms of hypersensitiveness such as drug fever or exanthema, on the occasion of a previous treatment should be desensitized before being again submitted to chemotherapy.

In the presence of renal diseases or of a disease which would be aggravated by polyneuritis, for instance, diabetes mellitus or alcoholism, the symptoms and signs viewed as calling for chemotherapy should be most critically assessed. If the patient manifests achylia, or if he has previously suffered from polyneuritis, one should proceed with still greater caution. If there are reasons to suspect the presence of deficiency of aneurin, it is advisable to take the necessary steps to compensate for this, preferably before the administration of sulfanilamide or any related drug. To put all cases under prophylactic treatment with vitamin B<sub>1</sub> does not seem to be indicated.

Polyneuritis due to sulfanilamide and related drugs contraindicates further chemotherapy.

Pains, paraesthesia or symptoms of even the mildest form of paresis manifested during the course of the treatment, should call for immediate discontinuance of the chemotherapy. The patient should be ordered to rest in bed for at least a few weeks, as it was demonstrated that physical exertion was injurious.

No effective therapy is so far available ensuring definite cure of polyneuritis of this kind. The patient should be given physical therapy, and the administration of aneurin and liver preparations should also be tried. If pains and paraesthesia are distressing to the patient, insulin treatment should be taken into consideration. In administering insulin the doses should gradually be increased until the patient manifests subcoma (Müller-Hegemann, Silfver-sköld).

### Summary.

The author reports 7 cases of polyneuritis which had occurred following chemotherapy. Of these, 2 were treated with uliron, 1 with sulfanilamide, 2 with sulfathiazole, 1 with sulfanilamide, sulfapyridine and sulfathiazole, and 1 with sulfapyridine. In the latter case there was relapse of polyneuritis after two years when the patient was subjected to treatment with sulfathiazole, in the course of which the clinical picture was similar to periarthritis nodosa.

Polyneuritis following the treatment with non-methylated sulfanilamide compounds seems to be more malignant than uliron and sulfamethylthiazole polyneuritis. The frequency of polyneuritis, however, is considerably higher following the treatment with uliron and sulfamethylthiazole than after the use of other non-methylated sulfanilamide compounds.

The possibility cannot be excluded that in certain cases polyneuritis develops as the result of a purely toxic damage of the nerve tissue; in general, however, an allergic reaction seems to be responsible for its development, as it happens in cases of polyneuritis following the administration of serum. A previous damage to the nervous system, deficiency in the secretion of gastric juice and in aneurin are factors which render the individual susceptible to this disease. Muscular exertion may cause a latent polyneuritis to become manifest.

Polyneuritis is a severe complication, which, as a rule, causes invalidity of several months duration, sometimes even for life. The prognosis of sulfanilamide polyneuritis seems to be unfavourable compared with that due to other reasons.

In order to prevent the development of polyneuritis, the patient should be subjected to treatment over as short a period as possible and intermittent administration of the drug should be avoided. Methylated preparations should not be used. A patient who on the occasion of a previous treatment had manifested signs of hypersensitivity, should be desensitized previous to renewed chemotherapy. Sulfanilamide polyneuritis contraindicates further chemotherapy.

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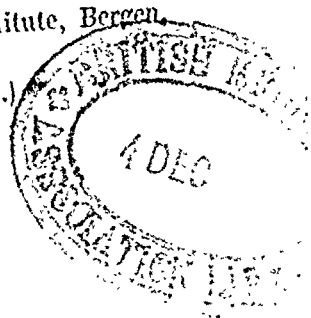
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cells is more probably induced by proteins set free from the infecting tubercle bacilli (2). The increased irritability of the hypersensitive cell continues for several generations of such cells grown in tissue culture (3). An essential condition for cellular irritability toward tuberculin is the presence of tuberculous tissue in the body (4) which again is produced both by living or dead tubercle bacilli (5). Hence the state of hypersensitiveness of cells from tuberculous animals is much more complex than the simple sensitization with tuberculo-protein or tuberculo-phosphatide inasmuch as animals sensitized to these crystalline substances do not react with tuberculin, or P. P. D., neither do they produce the Koch phenomenon when they are inoculated with living tubercle bacilli (6). On the other hand, tuberculous animals are more susceptible to heterologous bacterial filtrates (*B. coli*, *B. dysenteriae*, *B. typhosum*, etc.) than the normal animal (7). But attempts to immunize animals against a virulent tuberculous infection with tuberculin, tuberculo-protein or bacteria-free filtrates of tubercle bacilli have met with singular failure (8) even as sensitization with these substances has failed to produce a positive tuberculin reaction (9). A condition simulating a true tuberculin reaction may be produced in tuberculous animals sensitized to non-bacterial proteins, such as egg white or horse serum and the intravenous injection of these proteins may cause the death of tuberculous animals in a condition simulating tuberculin shock (10). But by and large it is becoming increasingly evident that the processes of immunization in tuberculosis are not identical with the processes of sensitization and that allergy, under no conditions, is necessary for protection in any stage of the disease. A considerable mass of experimental evidence has shown that no essential correlation exists between the degree of hypersensitiveness and the degree of relative immunity, either in man or in the lower animals, in a variety of infections, such as tuberculosis, syphilis, pneumococcal, streptococcal, staphylococcal and Pasteurella infections (11). In commenting on these important recent investigations, Rich (12) emphasizes that *«only statements and opinions have been offered up to the present (1937) by those who claim that hypersensitibility is necessary for immunity.»* Perusal of the war-restricted medical literature which has come to our attention up to November 1944, rather strengthens the truth in that emphatic statement.

From the Medical Department at the Chr. Michelsen Institute, Bergen,  
Norway.

(Chief: Konrad Birkhaug, M. Sc., M. D., F. A. C. P.)



## Allergy and immunity (iathergy) in experimental tuberculosis.

### XIII. Intradermal Spread of Vital Dye in Anergic, Allergic and Iathergic Tuberculous Guinea Pigs.

By

KONRAD BIRKHAUG and EINAR BERLE.

(Submitted for publication, January 2, 1945).

The study of allergy and immunity in tuberculosis continues to pre-occupy investigators and clinicians in many countries, to judge from the considerable annual output of articles on this subject. The consensus of opinion recognizes the great value of the dermal tuberculin reactions in the modern epidemiological surveys for detection of tuberculous infection. But the mechanism, significance and clinical manifestations of allergy and immunity in tuberculosis continue to baffle our comprehension. Before entering upon the report of our investigations on the intradermal spread of vital dye in anergic, allergic and iathergic tuberculous guinea pigs, which attempts to shed light on the mechanism of the dermal reactions with tuberculin, a few orienting remarks on the present knowledge of allergy and immunity in tuberculosis would not seem amiss.

Today it does not seem legitimate to consider the change in the sensitized cells of the tuberculous animal as due to an antigen-antibody reaction (1). The altered condition of the hypersensitive



cells is more probably induced by proteins set free from the infecting tubercle bacilli (2). The increased irritability of the hypersensitive cell continues for several generations of such cells grown in tissue culture (3). An essential condition for cellular irritability toward tuberculin is the presence of tuberculous tissue in the body (4) which again is produced both by living or dead tubercle bacilli (5). Hence the state of hypersensitiveness of cells from tuberculous animals is much more complex than the simple sensitization with tuberculo-protein or tuberculo-phosphatide inasmuch as animals sensitized to these crystalline substances do not react with tuberculin, or P. P. D., neither do they produce the Koch phenomenon when they are inoculated with living tubercle bacilli (6). On the other hand, tuberculous animals are more susceptible to heterologous bacterial filtrates (*B. coli*, *B. dysenteriae*, *B. typhosum*, etc.) than the normal animal (7). But attempts to immunize animals against a virulent tuberculous infection with tuberculin, tuberculo-protein or bacteria-free filtrates of tubercle bacilli have met with singular failure (8) even as sensitization with these substances has failed to produce a positive tuberculin reaction (9). A condition simulating a true tuberculin reaction may be produced in tuberculous animals sensitized to non-bacterial proteins, such as egg white or horse serum and the intravenous injection of these proteins may cause the death of tuberculous animals in a condition simulating tuberculin shock (10). But by and large it is becoming increasingly evident that the processes of immunization in tuberculosis are not identical with the processes of sensitization and that allergy, under no conditions, is necessary for protection in any stage of the disease. A considerable mass of experimental evidence has shown that no essential correlation exists between the degree of hypersensitiveness and the degree of relative immunity, either in man or in the lower animals, in a variety of infections, such as tuberculosis, syphilis, pneumococcal, streptococcal, staphylococcal and Pasteurella infections (11). In commenting on these important recent investigations, Rich (12) emphasizes that «only statements and opinions have been offered up to the present (1937) by those who claim that hypersensitivity is necessary for immunity.» Perusal of the war-restricted medical literature which has come to our attention up to November 1944, rather strengthens the truth in that emphatic statement.

Some confusion exists on the relationship of allergy to anaphylaxis in tuberculosis. Most investigators accept without reserve that tuberculo-anaphylaxis involves a separate mechanism from tuberculo-allergy inasmuch as the former is a true antigen-antibody reaction which is amenable to passive transfer (13). The abolition of tuberculo-anaphylactic sensitization by specific desensitization has failed to remove tuberculo-allergic hypersensitiveness (14). But one is not always clearly oriented on the fact that the tuberculin skin reaction both in man and in the lower animals may show a combination of anaphylactic protein hypersensitiveness and tuberculin specific hypersensitiveness. The former manifests itself by immediate edema which reaches maximum size in 24 hours and then completely disappears without leaving any trace of tissue injury. In excessively sensitized individuals presenting precipitins in the blood serum, a hemorrhagic skin reaction may appear which turns necrotic, with but a slight inflammatory reaction around the necrotic area. This reaction corresponds to the Arthus phenomenon in the rabbit, which species produce stronger antibody titer than does the guinea pig (15). The main characteristics of the tuberculin hypersensitiveness, on the other hand, are a delayed appearance (48—72 hours), central necrosis, absence of antibodies, impossibility of passive transfer, and always dependent on the presence of tuberculous tissue somewhere in the body. The tuberculous tissue, however, is not the direct source of the hypersensitive state nor of the increased antibody production which is responsible for the anaphylactic irritability inasmuch as when the antigen is injected directly into the tuberculous tissue, it leaves this and produces the effect elsewhere in the body (16). On account of the concurrent anaphylactic dermal reaction it is advisable never to read the tuberculin reaction before 48 hours have elapsed after the skin test was made in order to avoid confusing the protein reaction with the true and specific allergic reaction (17).

The mechanism by which tuberculin is retained within a strictly limited area of the skin in man or the lower animals infected with tubercle bacilli has been investigated extensively without any definite solution of the problem. Lurie (18) has shown that tuberculous animals display a protective capacity of restricting the spread of foreign materials such as agar and India ink, a feature which is lacking in the normal animal. In his important investigations on

the Arthus phenomenon, Opie (19) has shown that foreign proteins, such as crystalline egg albumin and horse serum, injected intradermally in rabbits sensitized to these, are localized at the point of injection and fail to enter the circulation. The subsequent dermal reactions are correlated with the antibody titer. Freund, Laidlaw and Mansfield (20) have shown that the sensitivity of tuberculous animals is unlike the Arthus phenomenon investigated by Opie because when the tuberculin dermal reaction disappears, the complement-fixing antibody titer remains intact. Bordet (21) and Freund (22) have extensively shown that BGC-immunized and tuberculous animals are both more susceptible to heterologous bacterial filtrates than normal animals.

What is apparently true of the altered skin condition of tuberculous animals toward specific and non-specific foreign material, holds also good for the viscera of tuberculous animals. Thus, Krause and Willis (23) have shown that if excised lymph nodes draining the site of inoculation of a normal animal are injected into other normal guinea pigs, the tubercle bacilli reach these nodes within 24 hours while in the reinfected animal it requires 2 to 3 weeks for the bacilli to reach these nodes. Boquet and Laporte (24), Dahl (25) and Birkhaug (26) have confirmed these observations of the protective barrier established in tuberculous animals against the spread of re-infecting bacilli. But Willis (27), Rich and McCordock (28), Siegl (29), Selter (30), Cummings and Delahant (31), Wilson, Schwabacher and Maier (32) and Birkhaug (26) have shown that mechanical obstruction to the spread of tubercle bacilli in the tuberculous animal is not dependent on the state of allergic hypersensitiveness inasmuch as it operates equally well in the desensitized organism. These investigations were carried one step further when Corper, Cohn, Damerow and Bower (33) and Birkhaug (34) were able to demonstrate the experimental separability of anaphylaxis, allergy and immunity in tuberculosis and when Birkhaug (35) succeeded in producing these three biological states in one and the same tuberculous animal and subsequently eliminated both the anaphylactic and allergic sensitizations without removing the relatively immune state. These observations justify the supposition that the altered condition in the viscera and the skin of tuberculous animals with respect to specific and non-specific foreign material is dependent on infection with tubercle bacilli but not necessarily

on the states of anaphylactic or allergic sensitization. These orienting remarks seemed essential as an introduction to the present investigation on the intradermal diffusion of isotonic vital dyes in anergic, allergic and iathergic (desensitized immune) tuberculous animals.

Hudach and McMaster (36) have made extensive studies of the spread of vital dyes in living tissues, under varying physiological and pathological conditions. They found the pontamine sky blue dye the most indiffusible for intradermal injection. The dye enters the superficial plexus of lymphatics through channels torn open or ruptured by the injecting needle. As little as 0.01 ml of the dye renders the lymphatics sharply visible at once. They have demonstrated that practically every true dermal dye injection is both interstitial and intralymphatic. Parson and McMaster (37) have further been able through small micropuncture wounds to make pure interstitial injections of vital dyes. In a series of experiments they have thus obtained material in which to study both the physiologic factors of diffusion and of normal lymphatic drainage.

Joyner and Sabin (38) made immediate use of the intradermal injection of the vital pontamine sky blue dye in order to study the influence of allergy in tuberculosis and epizootic lymphadenitis on the diffusion mechanism in the skin of guinea pigs. They found that there is a restriction both to the diffusion of the dye in the connective tissue spaces and to the drainage of the same dye into the lymphatics in guinea pigs suffering with the two mentioned diseases while the animals are allergic. In the skin of moribund tuberculous guinea pigs which were no longer allergic, the vital dye spread more rapidly than in the normal animal. They suggest that this altered tissue condition in the allergic state, combined with the fact that such changed permeability of the endothelium of the vessels, can be induced, even though in the reversed direction with tissue extracts (39), indicates the possibility of the presence of some general as well as specific factors in the allergic state. Further, they suppose that this property of restriction to the spread of the dye in the hypersensitive state may be a factor in concentrating the material injected into the skin and thus produce the localized tuberculin reaction.

In the present study we shall attempt to repeat this important work of Joyner and Sabin and likewise to extend it to include iathergic (desensitized immune) tuberculous guinea pigs.

### Materials and methods.

Three groups of normal guinea pigs, each consisting of 11 animals, weighing on the average 436 standard deviation 54.29 gms, were employed in the first series of experiments (Table 1). All these animals reacted negatively with 10 mg tuberculin injected intracutaneously. The group called Normal-Anergic was not infected with tubercle bacilli and retained only as normal controls. The group called Tuberculous Desensitized and Tuberculous Allergic were both inoculated subcutaneously in the left thigh with 0.000.1 mg virulent human tubercle bacilli («Tuxen»). By serial Löwenstein cultures this dose was found to contain approximately 19,000 viable tubercle bacilli (individual colonies). In a previous virulence determination experiment this dose killed 6 guinea pigs of the same age and weight in 122 standard deviation 38.14 days with generalized tuberculosis. The three animal groups were held under identical living conditions during the entire experiment. The group called Tuberculous Desensitized were injected subcutaneously with 100 mg crude tuberculin thrice weekly (every Tuesday, Thursday and Saturday) in order to render them as completely anergic as possible during the entire experiment. The control of this anergic state was made with 10 mg tuberculin intracutaneously every two weeks. When after 6 weeks we observed a slight erythema and induration (average 42 standard deviation 6.12 mm<sup>3</sup>) 48 hours after the test was made, we increased the desensitizing dose to 200 mg crude tuberculin thrice weekly, without unduly compromising the general health of the animals.

Exactly ten weeks after the virulent inoculation, we re-tested all the 33 animals in the three groups with 10 mg tuberculin intracutaneously. As indicated in Table 1 we found 48 hours afterwards that the Normal Anergic group gave negative reactions, the Tuberculous Desensitized group gave 37 standard deviation 18 mm<sup>3</sup> erythema and induration (nearly completely desensitized) while the Tuberculous Allergic group reacted with 845 standard deviation 181 mm<sup>3</sup> erythema and induration plus 123 standard deviation 41 mm<sup>2</sup> central necrosis. The condition of the skin was then found to be ideal for the testing of the diffusion of vital dye in the three groups of animals.

We are greatly indebted to Dr. Philip D. McMaster at the Rockefeller Institute for Medical Research for supplying us with 20 grams of purified pontamine sky blue dye and two of the Dewitt and Herz syringes used by Dr. Florence R. Sabin in her experiments (38) as well as a good supply of B—D needles No. 19 and Bishop needles No. 29. The dye had been dialyzed in running water until free from salts. On the advise of Dr. McMaster we made up very small amounts of a 2.16 percent dye in Tyrode's solution which strength is isotonic with blood. Joyner and Sabin made use of a 2.5 percent dye which was »approximately isotonic solution.»

Because of the great variability in the thickness of the fibrous layers of the dermis in the dorsal, lateral and ventral zones of the guinea pig, we made only use of the ventral area in all the subsequent dye injections. The hair was clipped with an electric clipping machine and then epilated with an aqueous mixture of barium sulphide and wheat flour and thereafter the skin was washed thoroughly in running lukewarm water. The dye injections took place the following day. The ventral zone was divided into four quadrants. Into the center of each was injected as close as possible 0.025 ml of the dye intradermally and always under the dissecting microscope in bright light. The plunger of the Dewitt and Herz syringe was lightly greased with »Lubriseal» and with an adjustable nut on the threaded plunger we trained ourselves to inject as small a quantity as 0.001 ml of the 2.16 percent dye intradermally and under oil with reasonable accuracy. The needle was brought a distance of about 2 mm just beneath the epidermis and the dye was injected very slowly and under gentle pressure during one minute. Another minute was allowed to elapse before the needle was withdrawn and in this manner the backflow of dye was minimal. This technique was strictly followed throughout the following experiments.

### Results.

The 0.025 ml dye forms a small bleb at the site of injection. The superficial lymphatics are filled immediately and even under the injection one observes the dye running through the larger lymphatics in long streamers which penetrate into the subcutaneous plexus. In the guinea pig the lymphatic trunks from the subcutaneous



*Chart 1.* N 1 and N 4: normal anergic guinea pig, and D 1 and D 4: tuberculous desensitized guinea pig, respectively one and four hours after the intracutaneous injection of 0.025 ml «Pontamine Sky Blue» vital dye in 4 separate areas.

plexus penetrate the panniculus carnosus muscle only opposite the regional lymph nodes (38). Besides the intralymphatic drainage of the dye, one observes a slow diffusion of the dye into the tissues surrounding the bleb which at the moment the injection was fi-



Chart 2. A 1 and A 4: tuberculous allergic guinea pig, and D 1 and D 4: BCG-immunized and tuberculous desensitized guinea pig, respectively one and four hours after the intracutaneous injection of 0.025 ml Pontamine Sky Blue vital dye in 4 separate areas.

nished measured about 2—3 mm in diameter. At the end of 15 minutes the diffusion of the dark dye measured about 4 or 5 mm in diameter and henceforth the spread of the dye was uniform in every direction from the bleb. The diffuse blue zone stood out sharp-



ly and could readily be measured. Like Joyner and Sabin (38) we found that measurements taken at intervals of 1 hour, 4 hours and 24 hours were adequate for purposes of comparison of the rate of spread of the dye in the various groups of animals. Charts 1 and 2 illustrate the spread of dye in the skin of normal and tuberculous animals after 1 and 4 hours. In the normal anergic, tuberculous desensitized and the BCG tuberculous desensitized guinea pigs the diffusion of dye became so extensive after 4 hours that the periphery of the faint blue zone made exact measurements rather difficult in contrast with the sharply delimited and distinct border of diffused area in the skin of the tuberculous allergic guinea pigs. Twenty-four hours after the injection of the dye, the borders of the diffused areas were still distinct in the allergic animals while the indistinctness of the faint blue peripheries of the diffused areas in the normal anergic and desensitized tuberculous animals made measurements extremely difficult. At this time all the mucous membranes in the latter animals were stained blue while this was not the case with the tuberculous allergic guinea pigs.

The diagonal measurements of the area of spread of the dye were made with a pair of callipers. These data are given in Table 1. We observe that no essential differences obtain between the measurements in the normal anergic and tuberculous desensitized guinea pigs in 1 hour, 4 hours and 24 hours after injection of the dye. The differences in the rate of spread were in no instance statistically significant between these two groups. But the rate of spread of the dye in the tuberculous allergic group was less than half that of the normal anergic and tuberculous desensitized guinea pigs in 1 hour, 4 hours and 24 hours after the injection of the dye. In every instance was this retarded spread of dye in the tuberculous allergic animals statistically significant from the simultaneous readings made in the normal anergic and tuberculous desensitized animals.

It was of interest to know if the immunization with BCG previous to the superinfection with virulent human tubercle bacilli on the one hand and desensitization of similarly treated animals on the other hand would alter the rate of spread of dye in the skin. Our second series of 40 normal and tuberculin negative guinea pigs weighed approximately the same as the first series, 453 standard deviation 42.8 gms. Ten animals were retained as *normal anergic controls* without any treatment whatsoever except the injections

Table 1.

*Diffusion of Vital Dye in the Skin of (1) Normal, Anergic, (2) Tuberculous, Desensitized and (3) Tuberculous, Allergic Guinea Pigs.*

Eleven Animals in each Group and each Animal injected Ventrally in Four separate Areas with 0.025 ml of a 2 Percent Pontamine Sky Blue Dye.

Time Interval	1 Normal-Anergic		2 Tuberc. Desensitiz.		3 Tuberc. Allergic	
	Mean	Standard deviation	Mean	Standard deviation	Mean	Standard deviation
	Sq. mm.		Sq. mm.		Sq. mm.	
1 Hour ....	526	91	439	171	233	82
4 Hours ....	918	68	920	126	425	86
24 , ....	1696	263	1575	362	695	119
Tested with 10 mg tuberculin	0	0	14	13.6	892	272
Probability						
Animal Groups	1 Hour		4 Hours		24 Hours	
	t	P	t	P	t	P
1 vs 2	1.492	0.27	0.046	0.90	1.279	0.25
1 , 3	8.133	< 0.001	14.992	< 0.001	12.500	< 0.001
2 , 3	3.614	< 0.001	10.734	< 0.001	7.652	< 0.001

with dye simultaneously with the remaining animals. Another group of 20 animals were inoculated intradermally on the dorsum with 2 mg living BCG on 3 occasions with one week's interval. Half of these BCG-vaccinated animals was immediately submitted to the same desensitizing regimen as the first series, namely 100 mg crude tuberculin injected subcutaneously thrice weekly. Two months later, the desensitized group reacted wholly negative with 10 mg tuberculin injected intracutaneously while the other 10 non-desensitized and BCG-vaccinated animals reacted with 964 standard deviation 178.16 mm<sup>2</sup> induration and 52 standard deviation 18.14 mm<sup>2</sup> central necrosis with the same dose of tuberculin. At this time we injected the BCG-immunized guinea pigs, plus a fourth group of 10 normal guinea pigs, with 0.000 1 mg virulent human tubercle bacilli (Tuxen) in the left thigh. The course of desensitization with tuberculin continued for the BCG-tuberculous-desensitized group. Eight weeks after the virulent superinfection,

Table 2.

*Diffusion of Vital Dye in the Skin of (1) Normal, Anergic, (2) BCG-Immunized, Tuberculous, Desensitized, (3) BCG-Immunized, Tuberculous, Allergic and (4) Tuberculous, Allergic Guinea Pigs.*

Ten Animals in each Group and each Animal injected Ventrally in Four separate Areas with 0.025 ml of a 2 Percent «Pontamine Sky Blue» Dye

Time interval	1 Normal, Anergic		2 BCG, Tuberc., Des.		3 BCG, Tuberc. All.		4 Tuberc. Allergic	
	Mean	Standard deviation	Mean	Standard deviation	Mean	Standard deviation	Mean	Standard deviation
	Sq. mm.		Sq. mm.		Sq. mm.		Sq. mm.	
1 Hour .....	440	73	455	142	201	101	221	48
4 Hours .....	1057	76	1075	251	623	223	697	160
24 " .....	1764	312	1623	387	1010	284	1025	125
Tested with 10 mg tuberculin	0	0	37	18	845	181	886	268
Probability.								
Animal Groups	1 Hour		4 Hours		24 Hours			
	t	P	t	P	t	P		
1 versus 2	1.482	0.217	0.445	0.550	2.020	0.05		
1 " 3	12.083	< 0.001	11.489	< 0.001	11.250	< 0.001		
1 " 4	15.552	< 0.001	12.001	< 0.001	14.130	< 0.001		
2 " 3	16.200	< 0.001	8.460	< 0.001	7.920	< 0.001		
2 " 4	20.250	< 0.001	7.650	< 0.001	7.155	< 0.001		
3 " 4	1.125	0.260	1.638	0.100	1.200	0.200		

the thrice weekly desensitizing dose was increased from 100 to 150 mg tuberculin. When all the four groups of animals were tested intracutaneously with 10 mg tuberculin 12 weeks after the virulent superinfection, we observed 48 hours later no reactions in the normal-anergic group, 37 standard deviation 18 mm<sup>2</sup> induration in the BCG-tuberculous-desensitized group, 845 standard deviation 181 mm<sup>2</sup> induration in the BCG-tuberculous group and 886 standard deviation 268 mm<sup>2</sup> induration in the tuberculous-allergic group. Thus, we had obtained the degree of anergy and allergy necessary for comparative study of the rate of spread of the vital dye.

In Table 2 we observe practically no difference in the rate of

spread of the dye in the skin of normal-nergic and BCG-immunized-tuberculous-desensitized guinea pigs in 1 hour, 4 hours and 24 hours after injection of the dye. The differences between the two groups fail to show any statistical significance. Again we observe a considerable restriction in the rate of spread of the dye in the skin of the tuberculous-allergic group. This retarded rate of spread is in every instance so low that it differs significantly from the rates recorded in the normal-nergic and BCG-immunized-tuberculous-desensitized guinea pigs. However, the retarded rate of spread of the dye in the skin of the tuberculous-allergic guinea pigs presents no statistically significant deviations from the rate recorded for the BCG-immunized-tuberculous-allergic guinea pigs.

A careful scrutiny of the data on the rate of spread of the dye and the degree of induration and erythema in the tuberculin reaction with 10 mg tuberculin failed to establish any statistically significant differences in the two sets of measurements in the tuberculous-allergic guinea pigs.

Four cachectic and moribund tuberculous guinea pigs which gave entirely negative skin reactions with 10 mg tuberculin injected intracutaneously, were subjected to 2 ventral injections with 0.025 ml dye. Table 3 shows the same pattern of diffusion rate in every one of these animals although considerable variations occur within the group. By and large, we observe that the rate of spread compares well with that seen in the normal-nergic and tuberculous-desensitized inclusive the BCG-immunized-tuberculous-desensitized animals.

Table 3.

*Diffusion of Vital Dye in the Skin of Moribund and Anergic Tuberculous Guinea Pigs*

Four Animals injected Ventrally in Two Separate Areas with 0.025 ml of a 2 Percent «Pontamine Sky Blue» Dye

Animals	1 Hour		4 Hours		24 Hours	
	Sq. mm.	Sq. mm.	Sq. mm.	Sq. mm.	Sq. mm.	Sq. mm.
K 19 ....	394	416	920	855	1380	1416
K 21 ....	350	402	760	608	1440	1476
K 22 ....	516	484	748	680	1152	1311
K 23 ....	416	496	924	918	1564	1418
Mean ....	434.3		801.7		1394.7	

## Discussion.

We have already called attention to the heightened non-specific irritability of hypersensitive cells, particularly in experimental tuberculosis. It is well-known that allergic inflammation brings to the site with greater readiness and in greater amounts all the elements of an inflammatory exudate, including antibodies, fibrin, granulocytes, macrophages and eosinophiles. These processes fix foreign proteins, bacterial products, and bacteria themselves at the site of inflammation, so that their penetration into the blood stream is prevented (40). It is not unlikely that the described altered condition of the skin in allergic animals which causes restriction of the spread of the non-specific vital dye, pontamine sky blue, may not eventually be linked up with the mechanism also possessed by allergic animals to concentrate and localize tuberculin either cutaneously in the Pirquet test or intracutaneously in the Mantoux test. The clinical parallel to the fixation of tuberculin in hypersensitive cells is the «flare-up tuberculin reactions» seen in diphtheria, scarlatina, morbilli, typhus, syphilis, etc. (41) where a temporary anergy supervenes on the acute infection. As soon as convalescence sets in, a «flare-up» occurs in the sites where the tuberculin test was made during the anergic phase. This altered condition of hypersensitive cells to concentrate and localize the specific substance tuberculin extends also to the nonspecific dye, pontamine sky blue, which Joyner and Sabin (38) and we have shown remains fixed to a strictly delimited area of connective tissue during 24 hours, without diffusing into the vascular tissues. These observations permit us to suppose that some general factor operates besides the specific factors which concentrate and localize foreign material in the hypersensitive tissue. In the non-immunized or immunized tuberculous animals which have been nearly or completely desensitized with tuberculin, we observed a normal and rapid spread of the intradermally injected vital dye through the connective tissue spaces, lymphatics and the larger blood vessels. Within 30 hours the stain had penetrated all the skin, mucous and serous membranes and the aqueous humor. Thus the lack of parallelism between allergic hypersensitivity and acquired immunity, as stressed in the introductory remarks of this paper, exists also in

regards to the spread of dye in the allergic and iathergic (desensitized-immune) tuberculous animals.

No satisfactory explanation can be formulated about this demonstrable change in the permeability of the endothelium in the lymphatics in allergically hypersensitive animals. The discussion appended to the paper by Joyner and Sabin (38) on this subject is quite suggestive but inconclusive. Our immediate interest centers on the demonstration by a wholly non-specific dye that allergic hypersensitiveness can be completely abolished from immunized tuberculous guinea pigs and that agreement thus exists between the results of the tuberculin test reaction and the vital dye diffusion. From our observations we may conclude that the intradermal spread of isotonic vital dye is somewhat inversely proportionate to the intensity of the local tuberculin reaction, even as Sewall, de Savitsch and Butler (42) have concluded that host-immunity is inversely proportionate to the intensity of the local allergic reaction. This latter conclusion was already formulated by Calmette (43) in 1927 and by Boquet (44) in 1932 and has been adequately confirmed by our extensive studies in iathergic immunity in experimental tuberculosis.

### Conclusions.

1. The skin of allergic tuberculous guinea pigs displays a restricting influence on the spread of a non-specific and isotonic vital dye, pontamine sky blue and the intralymphatic drainage of the dye is significantly slower than in the normal or moribund anergic tuberculous guinea pig.

2. The skin of non-immunized or immunized tuberculous guinea pigs, which have been desensitized during immunization and infection, displays no restriction to the spread of the dye and in this respect simulate the skin of normal animals.

3. A comparative study of the extent of the dermal tuberculin reaction and the diffusion of a vital dye in hypersensitive and desensitized iathergic immune tuberculous guinea pigs shows that the intensity of the tuberculin reaction is inversely proportionate to the spread of the dye.

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From the First Medical Clinic (Acting Head: Dr. Bo Ewert, M. D.) and the Second Medical Clinic (Head: Professor M. Odin, M. D.), Sahlgren's Hospital, Gothenburg (Sweden).

## **Hypothyreosis associated with severe intermittent claudication.**

Report of a case where the limping disappeared after thyroid treatment.

By

ERIC ERICSSON, M. B. and TORSTEN LINDQVIST, M. D.

(Submitted for publication February 9, 1945).

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When a patient seeks medical advice for intermittent claudication the history of the complaint is usually so distinctive that there need be no hesitation regarding the diagnosis. In the large majority of these cases it is possible also to detect objective signs of changes in the vessels of the leg. Cases are undoubtedly encountered, however, where no structural damage can be established [Lindqvist, (1)]. In this paper we are presenting a case of intermittent claudication in which the syndrome was apparently due not to structural changes in the arteries but to an etiologic factor of a more uncommon kind.

### ***Case report.***

B. B. A captain, born in 1893. Since his childhood he had been inclined to have pale cold hands in cold weather. In other respects he had been quite healthy until the present symptoms appeared. In September 1940 his knees had begun to swell a little, especially after exertion. At about the same time he began to experience pains in the lower legs when he walked. This discomfort gradually became worse until finally he was only able to walk a few hundred metres before having to stop on account of the intense pain. After resting for a while he was able to continue. When he

overstrained his arms he soon became tired but he had no pains in his arms. More or less simultaneously with the development of these symptoms his mental condition also changed. He had previously been an energetic vital man, but now he was becoming ever more fatigued. He was losing all initiative, and was slack and sleepy. He also noticed that he often felt chilled; and that he did not perspire. He was also experiencing some difficulty in speaking, he stammered occasionally and was often hoarse. As far as he could observe there had been no increase in weight.

The pains in his legs became so troublesome that he was unable to continue his service as an army captain, and on July 24, 1941, he was admitted to the second medical clinic of Sahlgren's Hospital.

The routine examination of the lungs, heart, abdomen, blood, and urine revealed nothing of interest. The blood pressure varied between 140/90 and 160/100 mm. Hg. Both knees were slightly swollen. His feet were cold and the dorsalis pedis artery was impalpable on both sides.

Chiefly because of his sluggish and apathetic behaviour, and an extraordinary alteration in his voice, it was suspected that he might have hypothyreosis. On July 30, 1941, the basal metabolic rate was found to be minus 30 per cent, and at a control five days later it was minus 37 per cent.

He was given thyroid treatment and an improvement was noted almost immediately. He began to feel livelier and stronger. Simultaneously with this improvement in his general condition we were surprised to find that the pains in the legs also began to disappear. By Aug. 22, 1941, he was able to run 150 metres without experiencing any pain at all in the calves. He was soon able to take up his military career again, and towards the end of 1941 he took part in cross-country marches of up to 30 kilometres at a time without discomfort. Since then he has felt perfectly well so long as he kept up the thyroid treatment. Sometimes, however, he neglected his treatment, and he then had a sensation of slight pressure over the calves during exercise.

No particular attention was paid to the condition of the peripheral arteries while he was in hospital, beyond what has already been mentioned, namely, that the dorsalis pedis artery could not be palpated on either side. At an examination at the beginning of October 1941, however, the pulse was palpated in all the normal places on the leg. An oscillometric examination carried out with a Recklinghausen apparatus gave tracings reaching about 50 mm from both calves. After exercise, the tracings increased in a normal manner [Lindqvist, (2)].

Measurements of the skin temperature in the toes, with a raised body temperature, carried out at the same time using a method described in other publications by one of the present authors [Lindqvist, (1, 3)], showed that when once the temperature had begun to rise in the toes it proceeded at a rapid rate, an elevation of about  $17^{\circ}$  C. being registered during the course of about ten minutes. The rise took place at approximately the same rate in all the toes. The findings from this examination are presented in figure 1. A control examination one week later gave on the whole the same results.

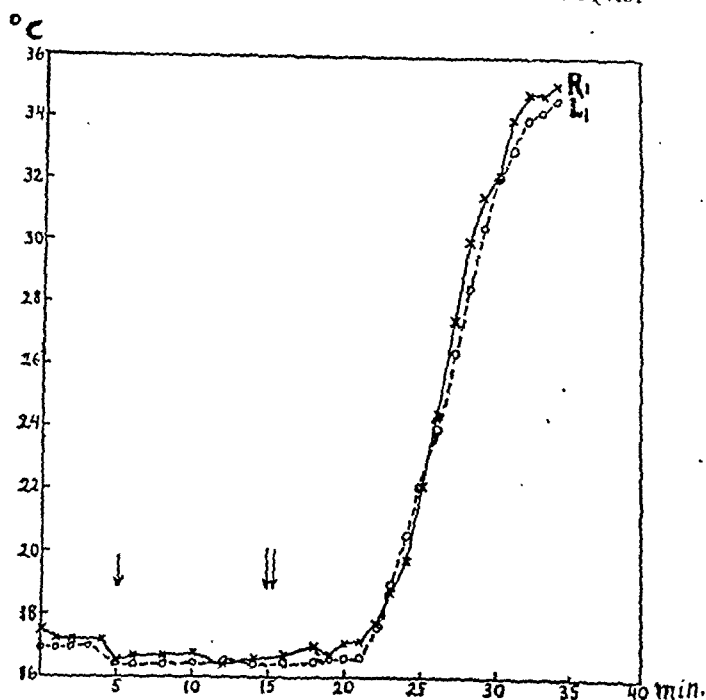


Fig. 1. The skin temperature in the terminal phalanx of the big toes. Before the recordings were begun the patient had been sitting with both his feet in water with a temperature of 15° C. At the point ↓ his trunk and thighs were immersed in a bath of water having a temperature of 40° C, with his feet and lower legs outside the bath tub. At ↓ ↓ the temperature was raised to 43° C. Temperature in the room, 15° C. R<sub>1</sub> = right big toe. L<sub>1</sub> = left big toe.

### Discussion.

When this patient complained of severe intermittent claudication his symptoms were so typical that it seemed obvious, at first, that structural disease of the arteries lay at the root of his discomfort. Added support for this assumption was provided by the fact that the pulses in the foot could not be palpated, a sign which, ever since the time of Erb (4), has always been taken to be the typical feature in intermittent claudication arising from structural arterial changes. It was only when the pains in his legs disappeared under the influence of the thyroid treatment that we began to wonder whether the intermittent claudication symptoms were due solely to his low basal metabolism or whether in addition there had existed structural changes in the arteries and a consequent decrease in the arterial circulation.

At the oscillometric examination on the calf, carried out after the thyroid treatment, the pulsations were so strong that it seems hardly likely that the flow of arterial blood to the muscles of the calf could have been impaired. [Cf. Ratschow (5), Philippides (6), Lindqvist (2)].

When the skin temperature in the toes was measured it was found that when all arterial spasm had relaxed the blood flow in the superficial vessels of the legs was normal. Such a rapid rise in the temperature as occurred in this case is never observed in patients in whom the arterial blood channels are obstructed. When the vessels are abnormally narrowed the curve relative to the temperature rise has an entirely different appearance, the upward trend being much more gradual.

Even without an arteriographic examination, therefore (for certain external reasons this could not be undertaken), we considered ourselves justified in concluding that there were no obstructive changes in the arteries that could have contributed towards producing intermittent claudication.

What then could the cause of this symptom have been? As it was not connected with structural disease of the arteries there is every reason for supposing that the genetic factor must have had something to do with his low basal metabolism.

In all probability, intermittent claudication is always to be regarded as a sign of an impaired blood flow arising in connection with exercise [cf. Lewis, Pickering and Rothschild (7); Lewis (8)]. We have found no mention in the literature of special investigations on the blood supply to the muscles in myxoedema. The pale cold skin observed in hypothyreosis is a sign of a poor circulation in the skin. There is no justification, however, for assuming categorically that because of this fact the supply of blood to the muscles is also poor [Grant and Pearson (9); Friedlander, Silbert and Bierman (10)]. As various investigators have proved, however, that the circulation in the peripheral vessels is lowered in general in hypothyreosis [Stewart, Deitrick and Crane (11); Wezler and Böger (12)], one feels fairly safe in concluding that the blood flow to the muscles must also be impaired in this disease. This must mean that the arteries are in a certain state of contraction. From observations made in Raynaud's disease, as well as in other forms of arterial spasm, we know that when arteries have attained a certain degree of contrac-

tion they do not respond as readily as they do normally to vasodilative stimulation. A mechanism of this kind may have been in question in the present case. This seems a more likely explanation than to assume that an arterial spasm of a similar type to that described in connection with another case [Lindqvist (1)] had arisen during exercise. Wezler (13) has demonstrated, however, that under certain circumstances drugs can have the opposite effect on vessels in patients with myxoedema compared to that in normal persons. In this way, a spasm might also arise.

The opinion advanced by Zondek (14), that the vasomotor centre would seem to be »dead» in myxoedema and that patients suffering from this disease »seem to lose their power of adapting the volume of circulating blood to their varying needs» (15, p. 186), certainly fits in well with the above arguments, but the experimental conditions upon which he based his conclusion were defective, and we are therefore unwilling to accept it as an explanation.

As far as we can find, there has been no previous description, either in the literature on intermittent claudication or in that on hypothyreosis, of a case similar to that presented in this paper. As an endeavour has been made to explain the patient's pains on the basis of his low rate of basal metabolism one cannot help wondering also why the same symptoms are not met with in all cases of severe hypothyreosis.

We are unable to supply a definite answer to this question but the following explanation seems to be feasible. As hypothyreosis develops in a patient he becomes more and more inactive and he consequently avoids all unnecessary muscular exertion. The patient described here was unable to spare his muscles owing to his military activities, and the lowering of his functional capacity therefore made itself more apparent than it would have done in a person able to make his own decisions as to his bodily movements.

Thus, the explanation of the patient's pains is hypothetical, but it seems undeniable that his low basal metabolism was the cause of his intermittent claudication symptoms. It may be useful to remember this possible explanation of intermittent claudication when dealing with cases where the symptoms can not be set down with certainty to structural disease of the arteries.

### Summary.

The authors describe a patient with intermittent claudication who was also suffering from severe hypothyreosis. The former condition disappeared after thyroid treatment. No signs of structural changes in the arteries could be discovered and it thus seemed as though the low rate of basal metabolism was the only explanation. A possible mechanism to account for the appearance of intermittent claudication is discussed.

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From the IVth Medical Service of St. Erik's Hospital and the State Bacteriologic Laboratory, Stockholm.

## Investigations into the Acute Infections of the Upper Respiratory Tract.

III. Studies of the influenza virus and concomitant infections during the winter and spring of 1944.<sup>1</sup>

By

GUNNAR LÖFSTRÖM.

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In previous papers (4, 8) studies were reported on the bacterial infections of the upper respiratory tract and acute pneumonia. The pneumococcal infection was investigated from the epidemiologic point of view particularly. The circumstances of the pneumococcal infection were interpreted as follows.

In closed population groups, e.g. in a military barrack, acute pneumonia constitutes the most serious manifestation of an epidemic of acute infections of the respiratory tract. The occurrence of pneumonia coincides with the climax of the epidemic but most cases of pneumonia generally occur during its regression. All types of pneumococci may be contagious and spread epidemically under favourable circumstances. They are not particularly contagious for healthy individuals. A primary pneumococcus infection gives rise to a catarrhal infection but does not cause acute pneumonia. In most cases the bacterial infection is preceded by a virus disease.

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<sup>1</sup> These investigations are aided by a grant from A. B. Astra, Södertälje, Sweden.

### *Investigations in 1944.*

The occurrence of the influenza virus during the winter and spring of 1944 was studied in cases of catarrhal infections in a Stockholm regiment, special attention being paid to the relation between the virus and bacterial infections.

*Scope.* Conscripts with acute infection of the respiratory tract and with a temperature of at least 38 C were studied. Patients with symptoms of influenza were made to gargle with about 20 ml. of 10 per cent serum broth. In every case throat swabs were taken for bacterial examination and blood samples were taken for serologic examination. A second swab test was made the day after the first test and further tests as needed. The blood tests were repeated every ten days. The serum samples of each case in which bacteria were found in the throat tests were examined for the presence of antibodies against the bacteria found. All serum samples were further examined for the presence of antistreptolysin and antibodies against influenza virus A and B. 153 patients were examined.

### **Methods.**

*Gargling fluid.* Inoculation experiments were made, as a rule, within a couple of hours after taking the samples. If this was not possible, the samples were kept in a cold cabinet, containing carbonic acid ice, at a temperature of  $-76^{\circ}\text{C}$ . Before inoculation the gargling fluid was centrifuged, the sediment was ground with quartz sand and again mixed with the supernatant fluid. After repeated short centrifugation 1—2 ml of the supernatant fluid was inoculated into a ferret intranasally under light ether anesthesia. The temperature of the ferret was taken morning and evening. If the inoculation took, as shown by rise of temperature on the second or third day, nasal catarrh and poor general condition, the animal was killed on the third day. The nasal mucous membrane and the nasal turbinals were removed and ground with quartz sand in 10 per cent serum broth to make an approximately 20 per cent suspension. After short centrifugation the supernatant fluid was inoculated into a new ferret.

If this ferret became infected it was treated in the same way



and after Seitz filtration the nasal mucous membrane suspension was injected into a hen's egg according to Burnet's method (2).

Gargling fluid was likewise inoculated directly into eggs after Seitz filtration.

Attempts were made to transfer the virus to mice, both with nasal mucous membrane suspension from a ferret, and directly with gargling fluid. Six mice were inoculated intranasally under light ether anesthesia. They were killed on the fourth day, and further passages were effected with suspensions of the lung tissue, although the latter failed to show any changes characteristic of virus pneumonia. If there were still no typical pulmonary changes by the sixth passage, the result was regarded as negative.

*Throat swabs.* The throat swabs were put into 1 per cent dextrose ascitic broth. After 6 hours' growth at 37 C the culture was streaked on a blood agar plate and a mouse was injected intra-peritoneally. The blood plate was examined the next day for the presence of hemolytic streptococci and *Hemophilus influenzae*. The type of streptococci was determined by Griffiths method (5). Cultures were made from the heart blood of the mice that died within 10 days on ascitic broth and a blood agar plate. The broth culture was examined according to Neufeld's method. The types of pneumococci were determined, insofar as the necessary factor sera were available, according to Kauffmann's and his associates' type scheme as published by Mörch (9).

*Serologic investigations.* Antibodies against the influenza virus A and B were determined by means of the complement fixation test according to Nigg, Crowley and Wilson (10). Virus-containing chorioallantoic fluid from virus-infected hen's eggs was used for the antigen. Between the experiments it was stored at -76 C. Virus A was a PR8 strain, obtained from Dr S. Schmidt, of the Danish State Serum Institute. The virus B strain had been procured from Dr Andrewes, of the National Institute for Medical Research, England.

*Agglutinins against streptococci* were determined by slide agglutination. The serum dilutions were made in physiologic saline solution mixed with 20 per cent horse serum.

*The antistreptolysin titre* was determined according to the method of Ipsen (6).

*Antibodies against pneumococci* were determined according to a previously described slide-agglutination method (7).

*Agglutinins against Hemophilus influenzae* were determined by the same method as the streptococcal agglutinins.

### Results of the virus investigations.

It was not possible with any certainty to prove the presence of virus in any of the gargling fluids. Only a few ferrets were available and the inoculations were made on a limited scale. Gargling fluids from nine cases which in eight cases serologically proved to be influenza A were tested. Three ferrets were used, two of them being inoculated with samples from four pooled gargling specimens (no:s 92, 96, 99, 100 in one sample and no:s 105, 106, 107, 108 in the other) and the third with a sample from one case (no 128). The three ferrets displayed similar symptoms. The first passage caused a slight rise of temperature on the third day, but no other symptoms. The second passage led to more pronounced symptoms, a moderately high temperature being already registered on the second day. The animals also got nasal catarrh and the general state of health was affected, but there were no pulmonary changes. Subsequent passages, on the other hand, yielded poorer results. Attempts to effect transmission to eggs and mice did not succeed in a single case. Here it should be remembered that British workers (1) did not succeed in transferring strains to eggs or mice from the epidemic that swept over England in November and December 1943. It is possible that the Swedish epidemic in April 1944 was a direct continuation of the English influenza epidemic, which might have reached Sweden via America, Italy, Germany and Denmark.

### Results of the bacteriologic examinations.

The bacteriologic findings are shown in Table 1. Only cases which were examined at least twice during the disease have been recorded.

The table shows that streptococci, pneumococci and *Hemophilus influenzae* were present in 117 out of the 153 cases examined, either separately or in combination. On the whole it may be stated that the various types of pneumococci occurred with the same fre-

Table 1.

The occurrence of various types of bacteria and of antibodies against virus and bacteria in tests taken from men of a Stockholm regiment hospitalized during the period 11th January—8th May, 1944 for acute infection of the respiratory tract.

Pl = Pneumococcus type 1, Sl = Streptococcus type 1, Ssp = spontaneously agglutinating streptococci, SO = Streptococcus of undeterminable type, Hi = Hemophilus influenzae, ASU = antistreptolysin unit, IA and IB = Influenzavirus A and B. INT = Insufficient Number of Tests.

Case no.	Date of onset	Types of bacteria	Antibodies										Disease agent		
			Acute-phase serum			Convalescent serum			Acute-phase serum			Convalescent serum			
			Day of dis.	Antibody	Titre, ASU	Day of dis.	Antibody	Titre, ASU	Day of dis.	Antibody	Titre, ASU	Day of dis.		Antibody	Titre, ASU
1	11/1	P9	1	P9	<1/2	9	P9	1/2	1	AS	288	9	AS	576	P9
2	"	P15													
3	"	Ssp+P18	1	AS	144	20	AS	1152							SO
4	12/1	P15+P32													
5	14/1	P15													
6	17/1	Ssp+P15	1	AS	72	12	AS	288							SO
7	"	P24	1	AS	36	10	AS	72							
8	"	P3	1	AS	72	1	AS	144							
9	"	Ssp+P7C			INT			INT							
10	"	P14			"			"							
11	18/1	O													
12	"	O													
13	"	S26													
14	19/1	P15+P32													
15	"	P16+P19													
16	"	P28													
17	"	O			INT			INT							
18	"	O			"			"							
19	21/1	P3+P19													
20	"	P19	1	P19	<1/2	7	P19	1/2							P19
21	"	O													
22	26/1	Ssp+P31	1	AS	144	17	AS	396							SO
23	"	P3+P12+Hi													
24	"	S1+P11													
25	"	P15+Hi													
26	"	P3+P25	1	AS	50	10	AS	100							



Table I. (Cont.)

Case no.	Date of onset	Types of bacteria	Antibodies										Disease agent		
			Abute-phase serum			Convalescent serum			Acute-phase serum			Convalescent serum			
			Day of dis.	Antibody	Titre, ASU	Day of dis.	Antibody	Titre, ASU	Day of dis.	Antibody	Titre, ASU	Day of dis.		Antibody	Titre, ASU
67	23/3	Ssp	1	AS	70	11	AS	140							
68	"	Ssp+P12													
69	"	O													
70	"	S3			INT			INT							
72	27/3	Ssp+P21													
73	"	S5	1	S5	<1/2	18	S5	1/128	1	AS	280	18	AS	560	S5
74	"	S5+P12+P31	1	S5	<1/2	15	S5	1/128	1	AS	100	15	AS	280	S5
61	29/3	P22	1	IA	<1/4	9	IA	1/16							IA
75	"	O													
76	31/3	S13+P8+P9	1	IB	1/4	11	IB	1/16	1	S13	1/8	11	S13	1/8	IB
78	3/4	Ssp	1	IA	<1/4	11	IA	1/32							IA
79	4/4	O													
80	"	P4	1	IA	<1/4	10	IA	1/64							IA
81	6/4	S4+P9	1	S4	<1/2	8	S4	1/2	1	AS	125	8	AS	250	S4
82	"	Ssp+P12	1	IA	<1/4	8	IA	1/32	1	AS	125	8	AS	250	IA
83	"	S5+P19	1	IA	<1/4	5	IA	1/16				11	IA	1/32	IA
84	"	O	1	IA	<1/4	5	IA	1/8				11	IA	1/32	IA
86	11/4	O	1	IA	1/16	14	IA	1/16							IA
87	17/4	P24													
88	"	S5—P24	1	IA	1/8	10	IA	1/64							IA
89	20/4	Hi	1	IA	1/4	7	IA	1/32	1	AS	560	19	AS	1100	IA
90	"	P9+P11+ P13+P28+Hi	1	IA	<1/4	7	IA	1/128	1	IB	1/8	7	IB	1/16	IA
91	"	P23	1	IA	<1/4	8	IA	1/64				30	IA	1/64	IA
92	"	S5	1	IA	<1/4	12	IA	1/16	1	S5	<1/2	12	S5	1/2	
			1	AS	280	12	AS	560							IA+S5
93	"	O	1	IA	<1/4	15	IA	1/128							IA
94	"	S6+P4	1	IA	<1/4	13	IA	1/32				30	IA	1/32	
			1	P4	<1/2	30	P4	1/2							IA
95	"	O	1	IA	<1/4	13	IA	1/256							IA
96	"	P34	1	IA	<1/4	13	IA	1/128				27	IA	1/128	IA
97	"	S5+P10A	1	IA	<1/4	13	IA	1/32	1	S5	<1/2	13	S5	1/32	IA+S5
			1	AS	70	13	AS	1100							
98	"	S5	1	S5	<1/2	11	S5	1/16	1	AS	140	11	AS	560	S5
99	21/4	Hi	1	IA	<1/4	12	IA	1/256	1	IB	1/16	22	IB	1/8	IA

Table I. (Cont.)

Case no.	Date of onset	Types of bacteria	Antibodies												Disease agent	
			Acute-phase serum			Convalescent serum			Acute-phase serum			Convalescent serum				
			Day of dis.	Antibody	Titre, ASU	Day of dis.	Antibody	Titre, ASU	Day of dis.	Antibody	Titre, ASU	Day of dis.	Antibody	Titre, ASU		
00	»	P28	1	IA	<1/4	13	IA	1/32								IA
01	»	S5+P9+ P10A+Hi	1	IA	<1/4	17	IA	1/64	17	S5	<1/2	29	S5	1/8		IA+S5+
			17	AS	280	29	AS	400	1	P9	<1/2	17	P9	1/2		P9+Hi
			1	Hi	<1/2	29	Hi	1/2								
02	»	P18B+Hi	1	18B	1/2	13	18B	1/2	1	Hi	<1/2	13	Hi	1/2		Hi
03	»	P1	1	IA	1/8	5	IA	1/64	5	P1	<1/2					INT
04	»	P4+Hi			INT			INT								IA+P1
05	22/4	S12+P9+P22	1	IA	<1/4	6	IA	1/32				34	IA	1/32		IA
06	»	O	1	IA	1/4	18	IA	1/16								
07	»	P1	1	P1	<1/2	17	P1	INT								
08	»	S1+P11+P24	1	IA	<1/4	10	IA	1/128								P1
09	24/4	S5+P3+P13	1	IA	<1/4	13	IA	1/128	15	S5	<1/2	29	S5	INT		IA
10	»	S1	1	IA	<1/4	10	IA	1/16								IA
11	»	P16			INT			INT								IA
112	26/4	S5+P4+P34	1	IA	1/16	8	IA	1/64	1	P4	<1/2	8	P4	1/2		IA+S5+
			1	P34	<1/2	8	P34	1/2	8	AS	200	23	AS	800		P4+P34
113	»	O	1	IA	1/32	9	IA	1/128								IA
114	27/4	P11A	1	IA	1/16	8	IA	1/32								IA+O
115	»	P4	1	IA	1/32	12	IA	1/32	1	P4	<1/2	12	P4	1/4		IA+P4
116	»	S5+P4	1	IA	1/64	11	IA	1/128	11	S5	<1/2	19	S5	1/16		IA+S5+
17	»	S5	11	AS	400	19	AS	800	1	P4	<1/2	19	P4	1/2		P4
18	»	S5	1	IA	1/64	11	IA	1/128				29	IA	1/32		
19	»	P28	11	S5	<1/2	29	S5	1/64	11	AS	280	29	AS	2000		IA+S5
20	»	P24+Hi	1	IA	1/128	12	IA	1/32								IA+O
21	28/4	O	1	IA	1/16	12	IA	1/8	1	S5	<1/2	12	S5	1/16		
22	»	Hi	1	AS	200	12	AS	560								IA+S5
23	»	O	1	IA	1/4	12	IA	1/16								IA
24	»	P2	1	IA	1/16	11	IA	1/16								IA+O
25	»	P9+P19+Hi	1	P2	<1/2	7	P2	1/16								P2
26	29/4	O	1	Hi	<1/2	10	Hi	1/2								Hi
27	»	O	1	IA	1/32	10	IA	1/32	1	AS	<32	10	AS	125		IA+O
			1	IA	1/128	13	IA	1/64								IA+O

Table I. (Cont.)

Case no.	Date of onset	Types of bacteria	Antibodies									Disease agent			
			Acute-phase serum			Convalescent serum			Acute-phase serum				Convalescent serum		
			Day of dis.	Antibody	Titre, ASU	Day of dis.	Antibody	Titre, ASU	Day of dis.	Antibody	Titre, ASU		Day of dis.	Antibody	Titre, ASU
128	21/4	S5+P7B	1	IA	1/4	9	IA	1/64	9	S5	< 1/2	27	S5	1/16	IA+S5 IA+O
			9	AS	64	27	AS	250							
129	30/4	P31	1	IA	1/64	8	IA	1/64							IA+O
130	"	S12+P24						0							
131	"	P13	1	P13	1/4	12	P13	1/2							P13+O
132	"	P3						0							
133	2/5	S5+P34	20	S5	<1/2			INT							
134	2/5	O	1	IA	1/4	8	IA	1/32							IA
135	"	S5+P9+P11	1	AS	90	10	AS	180							
136	"	O	1	IA	1/8	8	IA	1/16							IA
138	"	Hi	1	IA	1/16	17	IA	1/8							IA+O
139	"	S5	1	IA	1/16	10	IA	1/4	11	S5	<1/2			INT	
			1	AS	250	10	AS	700							IA+S5
140	"	P10A	1	IA	1/16	10	IA	1/8							IA+O
141	"	P10A+Hi	1	IA	1/4	7	IA	1/64	1	Hi	1/2	7	Hi	1/2	IA
142	"	S5+Hi	1	IA	1/4	9	IA	1/64	11	S5	<1/2			INT	IA+S5
143	3/5	O	1	IA	1/128	9	IA	1/64							IA+O
144	"	P11+P17													
145	"	Ssp													
146A	4/5	O			INT			INT							
146B	"	O	1	IA	1/128	18	IA	1/64							IA+O
147	"	P31+P33A	1	IA	1/128	11	IA	1/128							IA+O
148	"	Ssp+P33A			INT			INT							
149	"	O	1	IA	1/16	11	IA	1/16							IA+O
150	"	S5	1	S5	<1/2	11	S5	1/2	1	AS	64	11	AS	250	
151	5/5	S5													
152	"	S27			INT			INT							
153	"	S5+P31	1	IA	1/16	11	IA	1/16	1	S5	<1/2	11	S5	1/4	IA+S5
			1	AS	250	11	AS	500							
154	"	O													
155	"	S5	1	IA	1/16	11	IA	1/16	1	AS	110	11	AS	220	IA+S5
156	"	O	1	IA	1/16	10	IA	1/16							IA+O
157	"	O													
158	8/5	O	1	IA	1/16	8	IA	1/4							IA+O
159	"	S5	1	S5	<1/2	12	S5	1/32	1	AS	160	9	AS	500	S5
160	"	S14+P16	1	IA	1/16	17	IA	1/32	1	S5	<1/2	17	S5	1/32	
			1	AS	500	17	AS	900							IA+S5

quency as in healthy material. Types with a low number, which are specially apt to cause acute pneumonia, were rare. Type 1 occurred in two cases of pneumonia at the end of April. During the same period a case arose of catarrhal infection, caused by type 2. Of the streptococci, type 5 was predominant during April and May. Hemophilus influenzae was not frequently found.

It is difficult to decide which of the bacteria present were of etiological significance. Many seem to have been merely saprophytes of the mucous membrane, though the existence of a number of definite bacterial infections was proven by the serological examinations.

### Results of the serologic examinations.

For a type of bacteria to be regarded as the cause of an infection, I have required that antibodies against it shall have been present in the serum during the period of illness. The best criterion for this is the presence of antibodies in the serum taken in the convalescent stage, but a lack of them in the serum taken during the acute stage of the disease (acute-phase serum). A doubling of the antibody titre from acute-phase serum to convalescent serum has also been taken to indicate an infection.

Complement fixing antibodies against the influenza virus frequently occur in small quantities in human normal serum (3). In the event of actual infection the antibody content rises considerably above the normal values. It is generally assumed that if the serum gives a positive reaction in a dilution of 1:16 or higher, the patient has recently been through an infection (3). However the most convincing evidence of acute influenza is considered to be a rise in the titre from a low value in acute-phase serum to a value 2—4 times higher during convalescence. On the other hand, inapparent influenza infections are common. An increased antibody titre against the influenza virus both in the acute-phase serum and in the convalescent serum of an acute infection may be regarded as evidence of preceding inapparent influenza.

The agglutinin titre and the antistreptolysin titre were determined in the cases of streptococcal infection. The former seems to be specific in type. The latter likewise is a specific reaction but does not indicate the type. The agglutinin titre as an indication of strepto-



coccal infection was interpreted according to the general rules just described. The content of antistreptolysin in acute-phase serum depends on the extent to which previous streptococcal infections have preceded the current infection. If the convalescent serum taken about a fortnight after the acute-phase serum contains at least twice as high an antistreptolysin titre as the latter, then the infection investigated is probably a streptococcal infection. The diagnosis is supported by the demonstration of streptococci of a determinable type in specimens from the throat. Since normal serum hardly ever contains type-specific agglutinins against streptococci the presence of these antibodies is more indicative of a recent streptococcal infection than a high antistreptolysin content. This problem will be discussed in a subsequent paper. Table 1 shows the result of the serologic examinations.

The first case of influenza A (no 61) occurred on 29/3, and during April there were thirty-nine cases of the disease. Sixteen further cases were recorded during the first week of May. During the period 29/3—24/4 twenty-six acute cases of influenza A occurred, and subsequently six more the last one on 2/5. The entire epidemic was over in just over a month. As seen, the acute attack of influenza is characterized serologically by a rise in the antibody content during the first two weeks. The titre then declines slowly but in many cases it is still high after a month. Cases 83 and 84 show a distinct rise in titre after only five days from the onset of the disease, and the majority of these acute cases register a high titre on the tenth day. Inapparent influenza infections also occurred and in such cases the antibody titre fluctuated slightly during an observation period of from ten to thirty days. The first inapparent case (no 86) was diagnosed 11/4. The titre remained unchanged at 1:16 for a fortnight. During the entire period of the investigation twenty-four inapparent virus A infections were diagnosed.

During the period preceding the influenza epidemic proper, i.e. during the months of January—March, it was only in exceptional cases that antibodies against virus A appeared in titres of 1/4 and 1/8, and generally in the same titre in acute-phase serum and in convalescent serum. In not a single case was a titre of 1:16 or more obtained.

A raised antibody titre against influenza B was demonstrated in cases 76 and 90. Case 76 is possibly a case of acute influenza B,

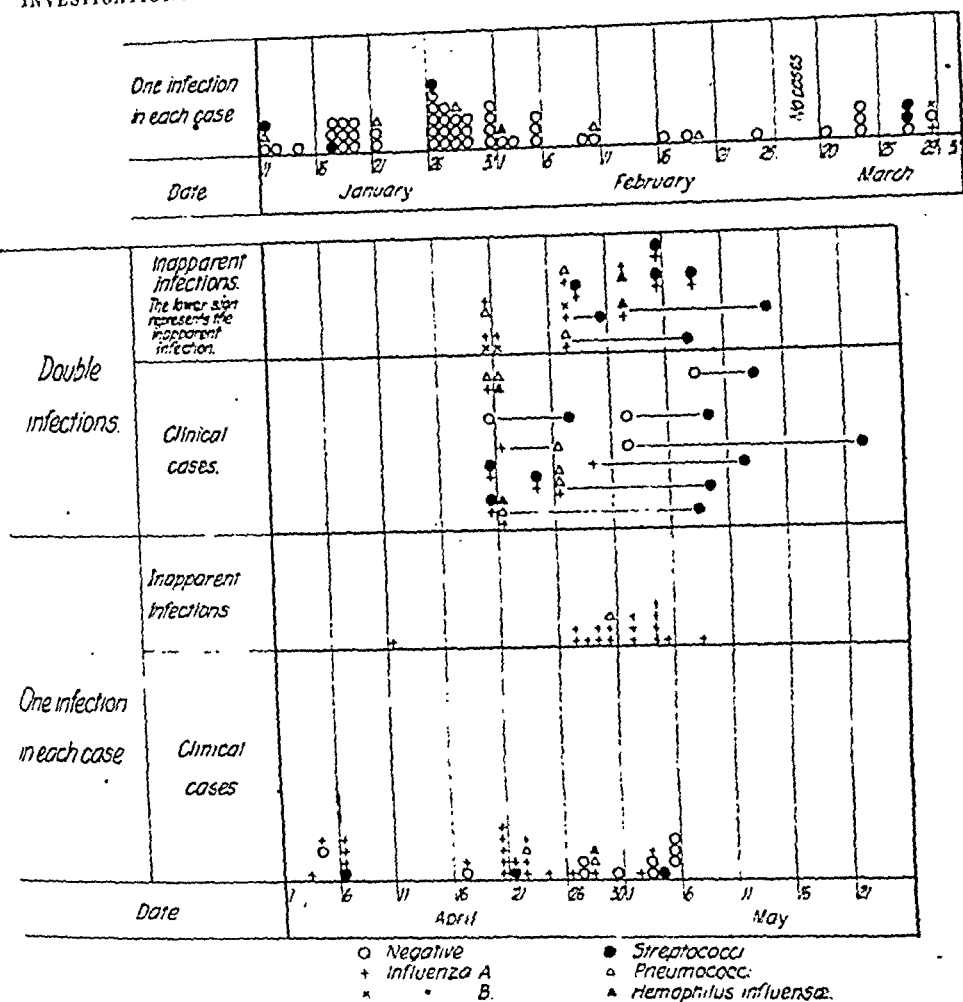


Fig. 1. Infections serologically verified and cases of unknown origin among conscripts who during the period 11/1—8/5 were admitted to the hospital suffering from acute infection of the respiratory tract.

though the rise of titre, from  $1/4$  to  $1/16$ , is perhaps too low to permit any definite conclusion based on one case only. Cases showing a serum titre of  $1/4$  and  $1/8$  against virus B were more common during the epidemic of influenza A than during the preceding months.

Of the bacterial infections those caused by streptococci of type 5 present the most interesting features. The first two serologically verified cases occurred on 27/3, and the subsequent epidemic of type 5 is closely related to the influenza epidemic which broke out at the same time. During the period 27/3—2/5 there occurred twenty-one definite cases of type 5 infections. This type of streptococcus



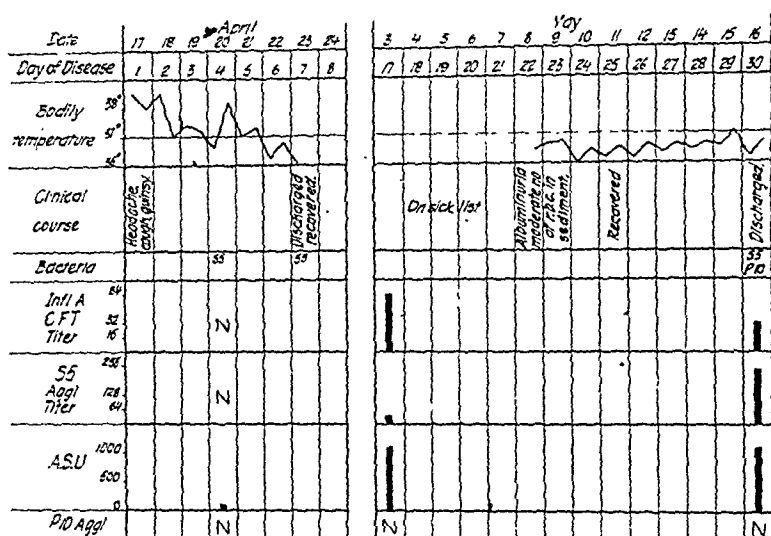


Fig. 3. Complex infection (case no 97) of influenza virus A + streptococci of type 5. C.F.T. = complement fixation test; r.b.c. = red blood cells. For further abbreviations see table 1.

mination. Thus, for instance, one of these cases (no 116) is a case of primary influenza revealed in conjunction with a complicating pneumococcal infection, and subsequently still further complicated by a streptococcal disease.

Fig. 2 shows a case (no 128) of typical influenza A complicated by streptococcal pneumonia.

A conscript fell ill on 28/4 with high temperature, cough and hoarseness. The throat was somewhat inflamed and examination of the chest was negative. He was admitted to the hospital, and after six days the temperature was normal, though he was still weak. He was discharged on 11/5 but remained on the sick list in the barracks. On 3/5 he again fell acutely ill with pneumonia on the right lung. In spite of sulphathiazole treatment the course of the illness was protracted. On 20/5 he was transferred to the Garrison Hospital, where the diagnosis was pneumonia + signs of a healed cardiac infarction. He was found unfit for further military service in July of the same year. The serologic and bacteriologic examinations show that primarily he fell ill with influenza A. During convalescence he was infected again, this time with streptococci of type 5, which resulted in acute pneumonia of a severe kind.

Fig. 3 shows a complex infection of influenza virus A and streptococci of type 5 (case no 97).

A conscript fell ill on the 17th of April with headache, coughing, tonsillitis and moderate fever. He was admitted to the hospital, apparently

got well rapidly and was discharged on 23/4. He was slow in recovering his strength and was again taken hospitalized on 8/5. He was tired and showed signs of nephritis. He was again discharged on 16/5.

The tonsillitis, which was the dominant clinical feature, was caused by streptococci of type 5. The simultaneous virus-A infection passed over without any typical symptoms, though it probably gave rise to the cough, which obscured the picture of typical acute tonsillitis. The streptococci of type 5 persisted for a long time in the throat and on the 21st day of the infection gave rise to the slight attack of nephritis. The agglutinin titre against the streptococci of type 5 rose slowly, whereas the antistreptolysin content went up rapidly and remained high for a long time. Complement fixing antibodies against virus A were diagnosed on the 17th day of illness.

### Clinical course of the diseases.

The typical, more severe cases of influenza during the epidemic in April-May exhibited relatively uniform symptoms of classic type: acute chill, general tiredness, coughing, pains over the whole body or in the calves, not infrequently accompanied by nasal catarrh or hoarseness. The throat was inflamed, but acute tonsillitis in the true sense of the term was invariably absent. Occasionally these primary cases also showed signs of bronchitis. The fever often followed an irregular course. Cases occurred of three or four days of high temperature, but in the milder cases, in which the symptoms were generally confined to coughing and cold, the temperature was low with only short spells of fever. During this epidemic many conscripts had periodical coughs and colds, though of so mild nature that they kept on duty. It was only when their illness assumed an acute form or when a fresh infection started that the initiating slight infection of the respiratory tract was revealed as inapparent influenza by the serologic tests.

The streptococci of type 5 accompanying the influenza gave rise to supervening diseases, which frequently proved severe and lasted a long time. For instance, there were six cases of acute pneumonia (nos. 101, 109, 118, 121, 128 and 142) verified by X-ray. Two of four mild cases of nephritis (nos. 22, 97, 116, 141) and one case of acute otitis (no 92) were also caused by streptococci of type 5. Three cases of pneumococcal pneumonia were diagnosed, one (no 9) in January and two (nos. 103, 107) in April. Case 103 was a virus-A infection followed by pneumonia caused by Pneumo-

coccus type 1. Case 107 occurred independently of the influenza epidemic.

These investigations confirm experiences gained earlier abroad to the effect that, clinically, influenza A cannot be distinguished from similar primary respiratory infections of a different origin. Chiefly in January, though also during the epidemic of influenza A and subsequently, there were a number of cases of clinical influenza which were not caused by virus A or B. Nor was it possible to discover any bacterial origin. They were apparently infections called influenza Y by American authors (11). From the clinical point of view, it is significant that these diseases were milder than influenza A, that as a rule their course was free from complications and that the whole illness lasted at the most a week.

In spite of the limited number of cases, this influenza epidemic vividly illustrates the advantage of individual isolation of influenza patients. During the epidemic there was no such possibility. The result was that six cases of nosocomial streptococcal infection (nos. 98, 109, 112, 118, 142 and 159) occurred during the period 27/4—13/5 among the patients admitted to the hospital as uncomplicated cases of influenza. These six conscripts contracted serious complications, four of which were pneumonia. Altogether 481 days of military service were lost.

### Discussion.

It has been possible by combined bacteriologic and serologic methods to analyse etiologically a number of cases of acute infections of the respiratory tract. An epidemic of influenza A complicated by infections caused by streptococci of type 5 form the essential basis of this study of the interplay between virus and bacteria. The results throw light on the causes of the heterogeneous disease picture characteristic of influenza and its concomitant diseases. It is well known that human beings react very differently even to the primary uncomplicated virus-A infection. Mild infections consisting of coughs and common colds and accompanied by slight fever alternate with severe, typical cases of influenza. These differences may be regarded as quantitative in contrast to the qualitative variations arising in the disease picture when bacterial infections intervene in the course of the disease. Case 97 in fig. 2 is an

example of a complex infection of this kind. Primary bacterial infections, such as typical acute streptococcal tonsillitis, occurred simultaneously with the virus diseases and their complications. Influenza B does not figure to any extent in the cases investigated — there may possibly have been one case —, whereas several cases of influenza Y (clinical influenza of unknown origin) is likely to have occurred.

Many bacterial respiratory infections may have evaded etiologic diagnosis owing to the fact that certainly not all bacteria of etiologic importance were isolated by the throat tests. Nor have many of the infecting bacteria demonstrated given rise to antibodies which could be shown by the methods used. It is probable, therefore, that only a relatively small number of the acute bacterial infections of the respiratory tract get etiologically diagnosed especially when the investigator insists upon the essential requirement of a serologic verification of the infection.

Unknown virus and non-diagnosed bacterial infections may therefore have arisen even in the cases here presented as having been thoroughly investigated, etiologically speaking. However, this would not affect the conclusions drawn herein.

### Summary.

A study has been made of the acute infections of the respiratory tract amongst conscripts belonging to a Stockholm regiment. An epidemic of influenza A occurred during April and May of 1944 and was complicated by infections of streptococci of type 5 arising epidemically. The diseases observed consisted of cases of typical primary influenza A, cases of primary streptococcal tonsillitis, cases of complex infection between virus A and bacteria, chiefly streptococci of type 5, and cases of influenza A followed by bacterial infection generally caused by type 5 streptococci. In addition, cases occurred which could not be diagnosed etiologically by the method employed, and among them were infections of the type known as influenza Y. The interplay between virus and bacteria was discussed.

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(From The State Bacteriological Institute, Stockholm, Head: Professor C. Kling).

## On the Occurrence of Poliomyelitis in a Parish in Middle Sweden — an Example of the Development of Endemic Centres.

By

RAGNAR SPAAK.

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During the summer and autumn of 1939 five cases of poliomyelitis with pareses occurred in the parishes of Kungsåra and Kärrbo in the province of Vestmanland (middle Sweden), four in the former and one in the latter. Simultaneously, a number of non-specific cases occurred which were suspected of representing an abortive form of the disease. The circumstances disclosed in the course of the epidemiological investigations would appear to command such general interest that I have deemed it justifiable to have them published.

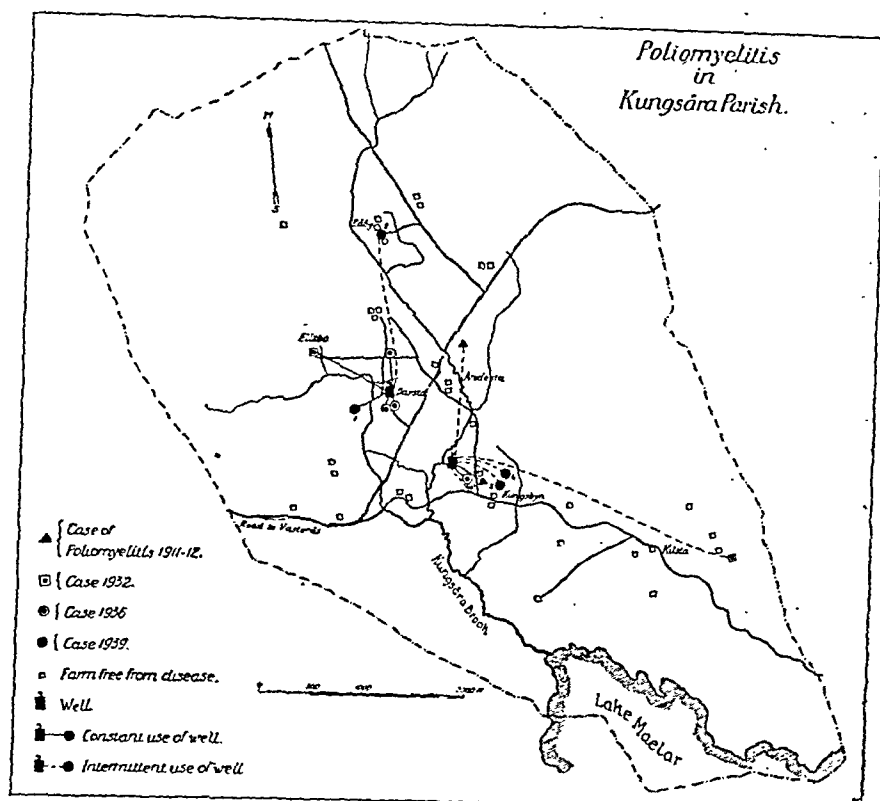
Kungsåra is situated at a distance of about 15 kilometres to the east of the town of Västerås on a bay of Lake Mälaren. The parish has a length of barely 10 km and an area of approximately 30 square km. On January 1st, 1938, its population was 370. The buildings are set wide apart and mainly placed along the middle part of a minor watercourse, a brook called »Kungsårabäcken», which runs diagonally through that area. The largest village is Kungsbyn, comprising some ten farms situated on a hill around the parish church. The outskirts of the area consists of bogs, swamps and woods, while the central parts, principally along the brook just mentioned, consists of arable plains with occasional stony hills.

The brook first appears as a big ditch, collecting water from swamps and woods in the northernmost part of the parish. Over the last three kilometres it grows wider and flows through a valley 10—20 metres wide, which gradually turns into marshes down by Lake Mälaren.

The first case of poliomyelitis in 1939 occurred on July 14th in the cottage of a farm-servant of Darsta farm, about 2 kilometres northwest of Kungshyn (see map!). The case was a typical one with pareses of the arms, back and legs (case No. 1). The next case of paresis (case No. 2) occurred as early as July 16th at Råby farm, a couple of kilometres north of Darsta. After that there was no fresh case until August 16th, when a young woman fell ill at Lindö farm, in the parish of Kärrobo. Lindö is situated about 7 kilometres as the crow flies from Kungshyn. This patient likewise developed pareses. The following two cases occurred at Kungshyn on August 28th and September 13th respectively. The first of these patients (case No. 3), a married woman of 27, had developed almost complete pareses in the arms and legs as well as a respiratory paralyse. The second case (No. 4), a 10 year old girl, not only displayed mainly cerebral symptoms (pareses of the external eye muscles) but also such signs of an affection of the medulla itself (the abdominal and patellar reflexes were all absent) that the diagnosis poliomyelitis will have to be regarded as correct. All the patients were female, their ages ranging between 10 and 27 years. The localization of the cases occurring at Kungsåra is evident from the map.

A non-paralytic case occurred round about July 25th at Darsta farm, but that case is not marked on the map, which only takes into consideration cases of paresis. Apart from this there had been several non-specific cases, which come under the heading «minor-illness». These are discussed below only when they refer to recognized cases.

The first question that arose was whether the cases of poliomyelitis occurring at Kungsåra represented an isolated source or if they should be regarded as a part of an epidemic more widely spread in the Västerås area. Up to October, 1939, a further 14 cases of poliomyelitis were met with in the district covered by the Isolation Hospital of Västerås. Of these cases none were so near Kungsåra as the one at Lindö. The nearest cases of paresis occurred during the period May 13th—September 19th in the town of Västerås,



14 kilometres from Kungsbyn. It proved impossible to demonstrate any positive direct contact between any of these cases of poliomyelitis and those at Kungsåra. In respect of the first case at Kungsbyn, i. e. the woman suffering from respiratory paralyse, there are, however, several possibilities of indirect contagion. Firstly, she had paid a visit to Västerås shortly before falling ill; secondly, her husband had carried out disinfection in the homes in which the first cases of the disease had developed. It should also be mentioned that the woman at Lindö had on two occasions — 4 and 2 weeks before she fell ill — been in personal contact with relatives resident in Kungsbyn and close neighbours of the patient just referred to. At that time no cases had as yet been reported in Kungsbyn. 25 days later, however, one of the relatives mentioned fell ill with raised temperature, diarrhea and a slight stiffness in the neck. As no medical examination was carried out in this instance it cannot be established for certain whether it was an actual case of non-

paralytic poliomyelitis. The probability of the patient at Lindö having carried the infection to Kungsbyn would not appear very great. It is more likely that the woman herself contracted the disease when visiting the place.

As regards the connexion between the cases of paresis occurring at Kungsåra the following facts have been traced. The wives in the two first afflicted families were on intimate terms and called on each other frequently. Only 12 days before falling ill the woman from Råby (case No. 2) had together with her 19 days old baby boy visited the family at Darsta, stayed the night and partaken of food and drink there during two days. At the time of her illness the infant had a cold (coryza and a slight cough) while the other members of the family were quite well. In the Darsta family no less than 4 of the remaining 5 members had, at the time the case of poliomyelitis occurred, been suffering from non-specific symptoms (inter alia stiffness in the neck, pains in the joints, poor appetite, vomiting). This family drew their drinking water from a pipe installed to supply the requirements of the Darsta farm. Probably the woman from Råby had also drunk of this water during her visit.

To my knowledge there had been no direct personal contact between these two cases and those at Kungsbyn. On the other hand the two Kungsbyn cases were almost daily in touch with each other until one of them fell ill. Each family had taken water from their own well but the two sick people had also occasionally had water from the nearby school. The young woman first taken ill was the daughter of the teacher and visited her parental home almost daily. The other patient attended the school. It proved that *the school, like the majority of the households of Kungsbyn, had, for some fifty years, drawn water from a spring called »bäckkällan», situated near Kungsårabäcken a few hundred metres away.*

The epidemiological circumstances reported above do not appear to afford any reliable support for either the contact theory or that of an alimentary or water infection. However, it is hardly probable that the contagion in cases No. 2 and No. 4 is due to contact with previous cases, as in both cases the contact took place *before* the falling ill of the earlier case. However, the possibility of water infection could not be excluded.

Being aware that some cases of poliomyelitis — in all 9 cases

with pareses — had occurred in the place before, I found it of interest to ascertain whether these could be connected with this year's cases. It proved that with a few exceptions they could, together with the cases of 1939, be referred to *two centres situated at Kungsbyn and Darsta*.

The very first case of poliomyelitis known at Kungsåra occurred in September, 1911, on a farm called *Ändesta* and concerned a 12 year old girl who attended the school at Kungsbyn. Thus, while at school, she may occasionally have drunk water brought from the spring. In February, 1912, a fresh case occurred when a 7 months old boy at Kungsbyn fell ill with uncertain symptoms but later proved to have got a permanent paresis of one of the legs. According to information now obtainable, the patient's family had, as a rule, taken drinking water from the same spring.

The next case at Kungsbyn did not occur until September, 1932. The family to which the patient belonged generally drew drinking water from their own well. However, the patient himself, a 10 year old boy, at that time attended the nearby school and may thus occasionally have drunk of the water from the same spring. A fortnight later an 8 year old boy, living at Kilsta,  $2\frac{1}{2}$  kilometres farther to the west, fell ill. This patient, too, attended the school at Kungsbyn. In both these instances the medical officer made an epidemiological investigation and established during his visit that no contact seems to have occurred between these and a case met with earlier in the Darsta centre. In June, 1936, a new case occurred at Kungsbyn, a 7 year old boy being afflicted with pareses. This case, too, was investigated epidemiologically by the medical officer, who could not establish any contact with other cases of poliomyelitis. Drinking water was obtained by this family from the same spring. In summing up it may be stated that *all the cases of poliomyelitis occurring over a number of years at Kungsbyn have been connected with one and the same water-supply*. Two of the patients had *daily* drunk of the water in question, while the other three cases within the centre, had, at the time of infection in all probability used the water occasionally. Another two cases *outside* Kungsbyn had probably used the spring water occasionally.

Of still greater interest are the previous cases of poliomyelitis met with at *Darsta*, the second centre. The first case occurred in 1932, when a 5 year old boy fell ill and developed typical parietic

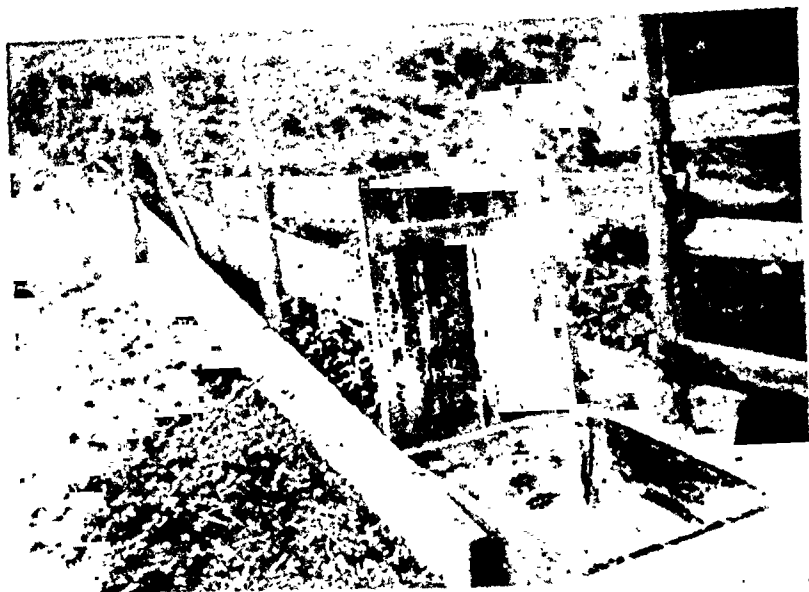


Fig. 1. »Bäckkällan». The spring near the brook.

symptoms; this case was the first one of the year within the district. His mother having passed away, the boy at the time lived with his paternal grandparents at *Elisbo*, a small croft about one kilometre northwest of Darsta. About one year after the boy's illness the father remarried and settled on a small farm just north of Darsta. Of the children born in the new marriage, a one-year-old girl developed poliomyelitis with pareses in August, 1936. It is possible that in this case the contagion had been transferred from Darsta farm, where two cases of poliomyelitis had occurred one month earlier. An examination of the supply of drinking-water in these two cases gave the following result: When the boy fell ill in 1932 the well at *Elisbo* was out of use and water was therefore fetched from the well of Darsta farm. At the farm to which the family had moved, the well was a very poor one, so water always had to be fetched from Darsta.

In the year when the just-mentioned little girl was ill, two of the children at Darsta farm developed poliomyelitis with pareses. In July, 1939, 10 days after the first case that year at Darsta, another case occurred in the same family, a nine-year-old girl being afflicted with headache, stiffness in the neck and a pronounced opisthotonos position. As the symptoms diminished in a couple of days no physician was, unfortunately, called in. However, there is



Fig. 2. The well in a field at Darsta farm.

every reason to believe that the case was a non-paralytic form of poliomyelitis. The family, of course, used the water from the Darsta well. *Thus it was proved that all the cases within the Darsta centre had used the one and the same watersupply at the time of infection.* In one case *outside* the centre it was proved that water from the supply in question was used occasionally at about the time of infection.

A few words remain to be said concerning the water-supplies involved. The water-supply common for the Kungsbryn cases, the spring, is found at the very edge of the little valley through which the brook Kungsårabäcken flows past the church. It is a small spring surrounded by a few boards and covered by a lid (see fig. 1) The spring itself lies on the border of the marsh forming the bottom of the valley. The level of the spring water was some decimetres above that of the brook flowing past at a distance of 12—15 metres. A small ditch from that part of the spring facing the brook facilitated the outflow from the spring. Due to the small difference in level, however, the spring must have been almost regularly polluted at high water by surface water from the brook. Samples of water from the brook showed a considerable pollution by colibacilli (230 colibacilli per litre according to the Eijkmann test at 46° C. and 2800 coli-aerogenes per litre according to the common lactose test at 37° C.)

The well used in the Darsta cases was situated in the middle of a field immediately north of the farm; it was stone-lined and well covered by a big stone-slab placed slightly higher than the surrounding ground (see fig. 2). Water had not been drawn directly from the well, which had been sealed, a pipe-line and a tank having been arranged to take the water to the house and cattle-shed. The neighbours had drawn water from a tap in the latter. A sample of the well water, analyzed by colititration, had a content of 10 coli and 230 coli-aerogenesbacilli per litre.

Samples from both the water-supplies and the brook were taken for tests for the possible presence of poliomyelitis virus. After concentrating the virus by a special method — which I don't intend to describe here — some monkeys were inoculated with the substance. The results of these investigations will be published later by C. Kling and his coworkers. I will only mention here that the monkey inoculated with the sample of water taken from the Darsta farm developed a slight paresis in one leg 12 days after the inoculation. After some days' further observation the animal was killed. The histological examination of the central nervous system disclosed changes typical of poliomyelitis (meningitis, perivascular infiltrates and neuronophagia). Through passage inoculation with the lymph glands from this monkey it was possible to produce a meningo-polio-encephalitis. The monkey inoculated with the sample of water taken from »bäckkällan» developed a weakness in the left hand on the 10th day after the inoculation and was killed after another two or three days. The histological examination showed meningitis and perivascular infiltrates in certain sections of the central nervous system. After passage inoculation similar changes mainly localized to the cerebrum were observed in the other animal. An additional monkey was inoculated with the water from the brook that passes the spring. This monkey showed no symptoms of disease, and at the postmortem it was quite normal.

### Summary.

In a small parish, Kungsåra, situated just north of Lake Mälaren in the middle of Sweden, 13 cases of poliomyelitis with pareses occurred during the period 1911—1939. An investigation of the epidemiological conditions proved that these cases could be refer-



red to two distinct centres, each localized around a certain water-supply. The investigation further showed that at one centre all the patients (5 persons) had daily used the water from the supply for drinking and domestic purposes at the time of infection. At the second centre the water from the supply in question had been used daily in two cases and only occasionally in the other three. The remaining three patients, who had fallen ill at places *outside the* centres, had probably made sporadic use of water from either of the water-supplies mentioned.

One of the suspected water-supplies consisted of a well-built, concrete-lined well situated in the middle of a field. The other was a natural spring, extremely badly protected from pollution by surfacewater. Bacteriological examinations disclosed fecal pollution of both.

After special treatment the water from both supplies was tested for poliomyelitis virus. When inoculated into monkeys both the samples of water produced clinical symptoms and pathologic-anatomic changes, well corresponding to the picture of experimental poliomyelitis (5).

### Discussion.

The most remarkable epidemiological feature in the cases of poliomyelitis described above is the tendency to the *development of endemic centres*. A similar concentrating of cases into endemic centres has also been observed by S. Gard in the course of epidemiological investigations in the provinces, *inter alia* in Bohuslän in southwestern Sweden (1).

The cases dealt with here appear to indicate that the cause of such a formation of centres may perhaps be found in the pollution of water-supplies by poliomyelitis virus. There is hardly any doubt but that in many places in Sweden the existing conditions favour the spreading of contagious matter present in water through wells and other private water-supplies. In an investigation into the hygienic conditions of the water-supplies in various parts of the country (carried out by a special committee of the Swedish Government Board of the Own-Your-Own-Home in 1941) it was established that out of 3,185 wells examined only 19 % were fully satisfactory from a hygienic point of view, while the remaining

81 % were impaired by one or more faults. No less than 69 % of the total number were insufficiently protected against pollution by surface water. The state of the wells varied considerably in different parts of the country.

During recent years a number of investigators have shown that poliomyelitis virus is present in the intestinal contents of poliomyelitis patients to a far greater extent than previously assumed. Thus, in 1940, Trask, Vignee and Paul (14) stated in a report of 111 tests for poliomyelitis virus in the faeces from poliomyelitis cases that 10 tests gave positive results when inoculated into monkeys. All the positive specimens were derived from the first four weeks of illness. When effecting intranasal instillations into monkeys according to their own method, Howe and Bodian (2) obtained typical experimental poliomyelitis with no less than 10 out of 14 fecal specimens from paralytic cases. Kramer, Gilliam and Molner (7) have demonstrated the presence of poliomyelitis virus not only in two sick children but also in the faeces from three healthy children and an adult nurse, all of whom had been in intimate touch with patients suffering from infantile paralysis. Several other investigators [Sabin and Ward (11), Lepine, Sedallian and Sautter (8)] have reported similar results.

In Sweden C. Kling has devoted special interest to this question in several publications (3, 4). On the basis of earlier Swedish experimental poliomyelitis material, subjected to renewed study, he states that poliomyelitis virus can be observed 2—3 times as often in intestinal contents as in pharyngeal secretions. In later experiments Kling, Olin, Fåhræus and Norlin (3) were able to prove the presence of virus in no less than 66.7 % of specimens of the evacuations from the seven first days of illness, while only 23.5 % of specimens from the 8th to 25th days of illness gave positive results. It would therefore now appear to be beyond doubt that poliomyelitis virus commonly occurs in the faeces of persons afflicted with an abortive or paretic form of poliomyelitis.

Where infantile paralysis virus is present in the faeces it may of course be expected that virus can be detected in sewage. Investigations in regard to the presence of poliomyelitis virus in sewage have been carried out by the American research workers J. R. Paul and J. D. Trask, partly in collaboration with the Swede S. Gard. In a publication dated 1940 (9) they state that during,

1939 they established the occurrence of poliomyelitis virus in sewage from two of three large up-country epidemics (Charleston, S. C. and Detroit, Mich). »From one of the sites it was found repeatedly. Both positive sites were located in the vicinity of isolation hospitals, and we believe that the findings indicate that this virus can be transported, for short distances at least, through the medium of flowing sewage». In the course of continued investigations during the summer of 1940 (8) positive results were also obtained in »a large sewer in New York City, which was not in the vicinity of an isolation hospital, although cases of poliomyelitis were present within the area this sewer drained».

Kling, Olin, Fåhraeus and Norlin (3) have, on two occasions, found poliomyelitis virus in the sewage in Stockholm. The positive specimens »were derived from a drainage area which had no communication with the sewer from the isolation hospital». The quantities of virus observed were very large. On account of this the last-mentioned investigators came to the conclusion that either a lot of people were carriers of the virus or the poliomyelitis virus can develop independantly in some other kind of organism than the human.

The first time a neurotropic virus quite resembling that of poliomyelitis was reported in drinking water was in 1940, when Professor C. Kling stated in a communication of The International Bulletin that he had discovered such an agent in a well at Oppmanna in Scania in the south of Sweden. In the autumn of 1939 7 cases of poliomyelitis occurred here, the first of which was a six year old boy from a solitary-lying farm,  $\frac{1}{2}$ —1 kilometre from the nearest neighbour. The family in which the case occurred had had no contact with any known cases of poliomyelitis. From the well, which was in a very poor condition (»dug well with walls of rubble; the lid over the well was broken and there was plenty of opportunities of the water getting fouled by the surroundings; the water itself was muddy»), a sample was drawn which was examined in the State Bacteriological Institute. After inoculation into monkeys the presence of an etiologic agent was established »which shows full likeness to the mild paralytic or abortive form of experimental poliomyelitis (with changes in the nervous system of the same localisation and of the same nature)». The etiologic agent demonstrated could be transferred to other monkeys and

could thus be regarded as being of an infectious nature. Later it has been possible to isolate (6) another four strains of a similar character. Two of these strains have been isolated from the water-supplies in the Kungsåra parish described above.

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## Observations on the hemoglobin content during war-time in seemingly healthy women.

By

A. M. RITALA.

(Submitted for publication February 22, 1945).

The severe food situation having continued for several years in Finland on account of the long war, it was to be expected that the consequences would be seen in a weakened state of health in the people. As a physician in a field hospital in 1943, I was able to observe the nurses' comparatively heavy burden of work and their monotonous food. I then decided to begin a systematic study of their hemoglobin content as, in a way, hemoglobin is one of the best indicators of the general state of health.

For the sake of comparison, the female assistants in the kitchens and wards of the same hospital and the female employees engaged in mending clothes were examined. The women examined were aged 20—45.

The tests were taken in a laboratory in the daytime with an adjusted Sahli-hemoglobin measurer (in which the normal point is 80). The determinations were always made by the same person who had received a laboratory training.

The clinical symptoms of anemia appeared in paleness, tiredness, ringing in the ears, palpitation, dyspeptic disturbances etc.

The hemoglobin results of the blood tests in different groups were as follows:

Hemoglobin Hgb	Number n	Average M	Mode Mo	Median Me
Nurses .....	17	64 (Sahli)	62 (Sahli)	63 (Sahli)
Kitchen and ward assistants .....	67	66 "	68 "	66 "
Those engaged in sewing	51	64 "	64 "	64 "
Whole material .....	135	65 "	65 "	65 "

Cases with the hemoglobin content under 60 (Sahli) were found in each group; the lowest amount found was 52 (Sahli). Nobody reached 80 (Sahli); the highest was 77 which was found among the kitchen assistants.

Thus, the whole material suffered from anemia, in its intensity at least about 15 Sahli-degrees lower than the normal state, on an average. The fixed proportions of the arithmetical mean, mode and median are a proof of the results not being caused by mere chance.

An etiological factor in these cases, besides deficient diet, is the actual loss of blood by menstruation which even in normal cases amounts to 2 ½—5 litres yearly, in menorrhagia cases still more. The female organism requires in order to keep fit, a greater amount of iron in food daily than does the male organism.

The author's opinion is that the hemoglobin content is too often omitted to be examined in women of mature age in our northern country. It is quite common to find gynecological patients suffering from hypochrome or posthemorrhagic anemia.

When comparing the above result Hgb 65 Sahli to that obtained in peace time, the hemoglobin level is found to be exactly the same as was ascertained by the author before the war in women from the poor quarters of Helsingfors during a pregnancy not properly attended to, after their having come for the first time from non-hygienic nutrition conditions to pre-natal care.

A woman suffering from chlorose and anemia becomes more or less an invalid as regards her working capacity. The author estimates that when the hemoglobin content has been reduced to:

Hgb 75—60	(Sahli)	=	<i>anemia levis</i> , the loss of working capacity is ab. 5—15 %,
» 59—50	»	=	<i>anemia media</i> , the loss of working capacity is ab. 20—30 %,
» ≤49	»	=	<i>anemia gravis</i> , the loss of working capacity is ab. 40—100 %.

Therapeutics, chiefly based on iron, may in these hypochromic anemia cases as a rule easily be carried out and lead to results. At the same time attention should be paid to other possible etiological questions like infections, function of the digestive channel etc. The development of social services and the improvement of general nutritional hygiene will destroy the origin not only of anemia but also of other signs of a weakened state of health.

### Summary.

Account of systematic studies in war-time concerning 135 women, not specially selected for the purpose, most of whom had been working in the remotest field hospitals for 2 years. Anemia was common: mean content of haemoglobin was 65 Sahli (= hgb 81 per cent = 11.2 g hemoglobin per 100 cm<sup>3</sup>). The nurses had the lowest hemoglobin content; a somewhat higher content naturally appeared among the kitchen assistants. The author deals with the question of etiology and loss of working capacity in the cases of anemia. In many cases, as far as this material shows, it must be estimated to have been reduced by as much as 25 %. He recommends a coherent system of definition for different degrees of intensity of hypochromic anemia.

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From Department III (Medicine) the Kommune Hospital, Copenhagen  
(Chief Physician: Poul Iversen, M. D.)

## Exophthalmic goiter after thyroid medication.

By

KNUD BRØCHNER-MORTENSEN.

(Submitted for publication January 2, 1945).

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As is well known overdosage of thyroid preparations is seen to be followed by some of the symptoms characteristic of exophthalmic goiter: loss of weight, tachycardia, palpitation, sweating, tremor, and nervousness. As a rule these phenomena make their appearance after a latent period of a couple of weeks, and most often they subside again fairly rapidly — in 2—3, at the most, 4 weeks — after the discontinuance of the thyroid therapy. In some cases the symptoms of intoxication persist for a longer period after the discontinuance of the thyroid administration and then subside gradually without particular treatment (2, 12, 16, 17, 18). In other cases, however, the symptoms of thyrotoxicosis are progressing after the discontinuance of the thyroid therapy, and eventually enlargement of the thyroid appears too, together with exophthalmus and other eye symptoms, so that here there appears to develop a lesion resembling a genuine exophthalmic goiter, not only in its symptomatology but also in its course.

This possibility has been realized in particular since Eggert Møller (13) in 1930 described a typical case of this kind and, in this connection cited a few previous brief casuistic reports from the literature, being thus the first to recognize the not infrequent occurrence of the lesion and discuss its pathogenesis thoroughly.

Subsequently, a number of such cases have been reported



in this country, so that up to the present a total of 10 cases has been presented here in Denmark (1, 3, 4, 5, 7, 11, 13, 14), while only relatively few cases have been reported in other countries [Stegmann (20), 1 case; Hurxthal (6), 7 cases].

Often these patients have presented a rather high degree of thyrotoxicosis. Of the above mentioned 18 patients, concerning whom the data have been fairly complete, 4 died soon with severe thyrotoxicosis [all Danish cases (5, 7, 11, 13)]. Thyroidectomy was performed on 10 of these patients; 3 improved under X ray treatment, and 1 improved somewhat under protracted medical treatment.

Generally the thyroid medicamentation in these cases was instituted on account of obesity, in a few cases on account of myxoedema, and in one case because of urticaria.

### Writer's Material.

To the patient material published so far, 4 additional cases may be added which were observed in the Kommune Hospital within the period of 1934—43<sup>1</sup>.

These four patients were women, aged from 25 to 58 years, who on account of obesity had been treated with thyroid preparations. Symptoms of thyrotoxicosis developed in direct connection with the treatment, and the lesion progressed after the discontinuance of the treatment.

The basal metabolic rate was found to be increased, showing values of 157, 134, 174 and 137 % respectively. Exophthalmus was not observed in any of them.

Thyroidectomy was performed on two of these patients. The remaining two improved under entirely medical treatment and on reexamination 9 years later they presented no sign of thyrotoxicosis.

#### Case 1.

Female, aged 25, wife of artist. Reg. No. Dep. II, 58—3/34.

Past history of good health. In October-November 1933, on account of obesity (weight 82 kg.), the patient was given thyroid treatment, 600 units<sup>1</sup> daily for three weeks, then 800 units daily for two weeks, and finally elityran for a couple of weeks. Under this treatment the patient lost con-

<sup>1</sup> I am greatly obliged to Dr. H. Heckscher, Chief Physician, for permission to publish 3 cases from Dep. II (Medicine).

siderable weight. At the discontinuance of this treatment she felt very tired and weak. She had frequent attacks of palpitation of the heart with restlessness and anxiety, sweating, nervousness, insomnia and, for some time, difficulty in swallowing. In spite of a good appetite she kept losing weight during the following months.

On admission, 20/2/34 (7 1/2 months after the discontinuance of the thyroid medication) the patient gave the impression of being very nervous. The skin was red, moist and warm. There was tremor of the hands and tongue. Eyes staring. Joffroy's sign positive. Thyroid diffusely enlarged, of soft consistency, vascular thrill. Circumference of the neck 35 cm. Right wrist 16 cm. Pulse 120. Blood pressure 160/85. Basal metabolic rate 157 % (patient somewhat restless during the determination). Weight 59.3 kg. Height 162 cm. Under confinement to bed and iodine therapy for about 5 weeks the patient became somewhat quiescent and gained 5 kg in weight. At her discharge her pulse rate was 80, the basal metabolic rate 123 %.

On reexamination, summer 1943, the patient stated she had been feeling well since her discharge from the hospital. Her weight had increased to 86 kg. There was no palpitation, sweat or nervousness, but a slight tremor. No thyrotoxic eye symptoms. The thyroid was rather large, soft. Circumference of the neck 39 cm, right wrist 17 cm. Pulse 96. Electrocardiography: Normal findings. Basal metabolic rate 105 %. Since her discharge from the hospital the patient has not received any treatment, neither iodine nor X-ray.

## Case 2.

Female, aged 51, wife of workman. Reg. No. Dep. 11, 19—6/34. Past history of good health. Menopause in 1932.

Ten months before admission, thyroid therapy was instituted on account of obesity, with a daily dose of 400 units, kept up for a period of 6 months. Under this treatment the weight decreased from 82 to 70 kg. After discontinuance of this treatment her weight kept decreasing and she lost 10 kg more; at the same time she became increasingly nervous, having tremor and palpitation of the heart. On admission, 15/5/34 she presented marked anxiety and pronounced tremor of the hands. The skin was warm and sweating. No definite thyrotoxic eye symptoms. Slight enlargement of the right lobe of the thyroid, of firm consistency. Pulse 80—90. Blood pressure 140/90. Weight 60 kg. Height 158.5 cm. Basal metabolic rate 134 %.

Under treatment with sedatives the patient quietened down in the course of 6 weeks. The weight was stationary and the pulse rate decreased to 70. At her discharge from the hospital the basal metabolic rate was 125 %.

On reexamination, summer 1943, the patient stated she had been able to work ever since her discharge. Still, she has been somewhat nervous con-

<sup>1</sup> 1 hormonal unit means the amount of thyroid preparation which in biological tests has the same effect as 0.001 mg thyroxin.

tinually, and she has lost a good deal of her hair. Her weight has increased to 78 kg. There is no thyrotoxic habitus, no eye symptoms, enlargement of the goiter, tremor or sweating. Pulse 80. Basal metabolic rate 101 %. Since her discharge from the hospital the patient has not received any treatment, neither iodine nor X-ray.

### Case 3.

Female, aged 48, wife of greengrocer, Reg. No. Dep. II, 778/42. Past history of good health. Menstruation ceased in spring 1941.

For several years, gradually increasing obesity. Three years before admission, institution of thyroid therapy, 600 units daily, lasting for about 1 ½ months. Under this treatment the patient lost about 5 kg in weight, but the treatment had to be discontinued on account of a sensation of precordial oppression, palpitation of the heart and nervousness. After the discontinuance of this treatment the patient at first felt somewhat better, but the loss of weight continued — she lost 20 kg more — through the following three years, and gradually she had increasing nervousness, palpitation of the heart, sweating and tremor.

On admission, 7/4/43, the habitus of the patient was typically thyrotoxic. Psychic and motor restlessness; warm moist skin with lively vascular reflexes. No thyrotoxic eye symptoms.

Thyroid distinctly enlarged, of firm consistency, with adenoma of the right lobe. Vascular bruit. Circumference of the neck 32.5 cm, right wrist 15.5 cm. Carotid pulsation markedly increased. Pulse 100, regular. Electrocardiogram normal. Blood pressure 160/90. Metabolism 174 %. Weight 63.3 kg. Height 155 cm.

Under X-ray and diiodotyrosin treatment the metabolism subsided to 120 %, and on 20/5 the patient could be transferred to surgical department for thyroidectomy.

### *Microscopy of Specimen from Operation: (Warschu).*

Sections from all three lobes of the thyroid show uniform changes. Both micro- and macrofollicular areas are seen, also more adenomatous areas where the lumina are quite small or altogether absent. The follicles are varying in size, most often polygonal, with well-staining colloid content. Marginal vacuoles are seen but seldom. The epithelium is middling high, with round or oval, apparently normal nuclei. Here and there some slender projections. No increase in the amount of interstitial connective tissue, but several areas of round-cell infiltration. No sign of tuberculosis or malignant newgrowth.

Microscopic diagnosis: Micro- and macrofollicular exophthalmic goiter (with histologically slight reaction to iodine therapy).

### Case 4.

Female, aged 53, single, telephonist. Reg. No. Dep. III 554/43. Past history of good health. Menstruation ceased in 1940.

In 1934-35, thyroid therapy on account of obesity, with a daily dose of up to 4 tablets No. IV (1600 units) — a total dose of several thousand tablets.

The treatment was discontinued for economical reasons, but ever since the patient had palpitation of the heart, increasing nervousness and tremor. During the last six months the symptoms increased greatly in intensity, and the patient lost 11 kg in weight. Profuse sweating.

On 12/3/43 the patient was admitted to the Psychiatric Dep., where her basal metabolic rate was measured to be 140 and 137 %. On her transfer to the Med. Dep. on 24/3, her habitus was typically thyrotoxic. Skin red and warm, with pronounced dermatographism.

No definite thyrotoxic eye symptoms. No distinct enlargement of the thyroid. Fine rapid tremor of the hands. Pulse 64, regular, Electrocardiogram normal. X-ray examination: Slight dilatation of the heart. Blood pressure 155/85. Weight 62.4 kg. Height 165 cm.

Under iodine treatment the basal metabolic rate decreased to 121 %, and on 11/4 the patient could be transferred to the surgical department for thyroidectomy.

#### *Microscopy of Specimen from Operation (Kjær).*

Sections from the thyroid show several large, somewhat grouped, close-packed follicles. The epithelium is cuboidal, in a single layer, more flat in many places, especially in the middle and left lobes. In the right lobe it is generally somewhat higher, often with ridges or projections, besides marginal vacuoles in the otherwise homogeneous and well-staining content.

The right lobe presents here and there some small parenchymatous areas. The stroma contains several clusters of lymphocytes, here and there larger accumulations of such cells, but otherwise no particular abnormality. No sign of tuberculosis or malignancy.

Microscopic diagnosis: Exophthalmic goiter (with fairly strong histological iodine reaction).

### Discussion.

In the course of time, various views have been advanced concerning the connection between thyroid medicamentation and the development of toxic goiter.

It does not seem very likely that it might be a matter of accidental coincidence when a direct transition has been observed from medicamentary thyrotoxicosis to florid hyperthyroidism. No doubt this combination has been far more frequent than would correspond to an accidental coincidence, and the number of such cases described is hardly likely to give any impression of the real frequency of such cases. The incidence of this phenomenon will depend on the attention paid to this possibility. Thus Eggert

Møller (15) found 2 cases among 150 patients with exophthalmic goiter and Thune Andersen (1) found 3 cases of this kind admitted in a little over one year to one medical department.

On the background of the extensive employment of thyroid preparations in the treatment of patients with obesity, however, these cases are so infrequent as to suggest that it requires a certain disposition in the patient if thyroid medication is to give rise to hyperthyroidism. Most of the cases reported in the literature have developed in women at or over the climacteric age, but this relation is probably due merely to the frequent occurrence of obesity just in this age-class. Indeed, instances of this lesion have been described also in younger women (3, 4, 6, 20 and our Case 1) and even in two men (17, 18). In the cases of the latter category, however, the symptoms subsided spontaneously within a few months.

The development of these cases appears not to be dependent on the amount of thyroid given the patient nor the duration of the treatment. In some patients the affection develops after a rather moderate medicamentation. Thus one of Eggert Møller's (13) patients received 300 units daily for a little over one month and about 6 months later she died with severe thyrotoxicosis, while one of Thune Andersen's (1) patients had received 1200—2400 units daily through 1 year.

It is hardly practicable on the basis of our present knowledge to explain how the administration of thyroid might give rise to a lasting hyperfunction of the thyroid glands.

It is the prevailing view that thyroid preparations either have no effect on the thyroid gland or that perhaps they lower the functions of the gland.

In histological studies on the thyroid, however, Krogh, Lindberg & Okkels (9) found one specimen to present features resembling those characteristic of toxic goiter, and this specimen was obtained from a patient who had taken altogether 1.4 kg of dried thyroid in the course of 5—6 years. In experiments on guinea-pigs no changes were found in the thyroid after peroral administration of dried thyroid tissue or subcutaneous injection of thyroxin for one week. Peroral administration of dried thyroid tissue for 8 months resulted in accumulation of colloid in the alveoli of the thyroid and slight atrophy of the follicular epithelium.

The possibility has been considered that the administration of thyroid might give rise to a dysfunction of the pituitary with increased production of thyrotropic hormone. But as far as I have been able to find out, there is no experimental basis for this hypothesis.

It has further been emphasized as a probable possibility that thyroid administration might bring about an abnormal function of the vegetative nervous system which then would stimulate the thyroid to increased function (13).

Possibly these cases come about as the result of several cooperative factors. In animal experiments it has been practicable to produce exophthalmus by administration of various substances stimulating the sympathetic nervous system — *e. g.*, ephedrine. The dose required for this effect is decreased by simultaneous administration of thyroxin, which in itself has no such effect (8). Corresponding phenomena have been observed in man in a few experiments (10, 19).

All told, however, it is hardly possible at present to give any satisfactory explanation of the fact that thyroid administration in certain cases is followed by the development of exophthalmic goiter. Still, the mere possibility of the development of such cases — apart from our knowledge of other risks — makes it reasonable to hold that the employment of thyroid preparations in the treatment of patients with exogenous obesity has to be abandoned.

### Summary.

A report is given of four cases of Gravis disease which developed in direct connection with thyroid treatment for obesity.

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From the Medical out Patient Department, Rigshospitalet, Copenhagen.  
Director: Professor Dr. Med. Eggert Møller.

## The Smooth Tongue.<sup>1</sup>

By

MOGENS FABER.

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It is part of the routine physical examination of a patient with an internal complaint to examine the oral cavity. When the complaint is not localized to this place the examination will in all essentials involve the conditions of the teeth and the surface of the tongue. As a rule, the examination of the tongue is very cursory, and the findings are of no great significance except in special cases.

When examining the tongue one pays attention to the appearance and the extent of the coating, especially as an indication of dehydration or an acidosis (Kirk), and one will look for signs of atrophy of the papillae of the mucous membrane. In rare cases the mucous membrane, and then especially the papillae, may be edematous, either universally or more localized. In other words, the main interest concerns the appearance of the papillae, or their possible absence.

This is quite contrary to what the physicians used to think regarding the conclusions to be drawn from an examination of the surface of the tongue. To the old-time physician the appearance of the surface of the tongue meant a great deal, especially, perhaps, in the diagnosis of diseases of the stomach. One remembers the saying »the tongue is the mirror of the stomach». It was mostly the increased coating which in this connection was watched with interest. Today,

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however, it is actually so that the physician is not so much interested in the coated tongue as he is in the very opposite phenomenon, the smooth tongue. That the coated tongue has lost most of its significance — except for a group of self-interested neurasthenics — is, *inter alia*, due to Fuchs (1898) who very clearly demonstrated that an increased coating of the tongue first of all is due to a reduced mechanical cleaning of the tongue. Thus it is a purely local phenomenon, and cannot justify any conclusion as to a simultaneous morbid process in the stomach. The explanation of the earlier belief is found in the fact that the coating increases during the anorexia which is associated with acute gastritis.

The meaning of the smooth, atrophic mucous membrane of the tongue is not yet understood. Since the interest in the phenomenon is growing it seems reasonable to subject it to a closer scrutiny.

### Earlier Investigations.

#### *Etiology.*

The significance of the non-coated tongue was actually not realized until after the publication of Hunter's monograph (1901) on pernicious anemia. Hunter described how in several cases of typical pernicious anemia he observed an affection of the tongue. Subjectively, this affection was characterized by pain, frequently rather severe, and especially pronounced during eating. On the tongue itself he observed red patches, almost void of mucous membrane, frequently with fluid-containing vesicles, and primarily localized to the tip and the margin of the tongue. In between these patches the mucous membrane was generally smooth and atrophic, but never as red as the patches. Hunter considered this affection of the tongue characteristic of pernicious anemia.

Prior to Hunter several authors had noticed the frequent affection of the tongue in pernicious anemia. Thus it is mentioned in some of the cases related by Müller, Laache, Eichhorn, Hale-White, and Bramwell. The earliest mention of the phenomenon as associated with anemia, undoubtedly inclusive of pernicious anemia, must be attributed to Dawson (1846).

The glossitis in pernicious anemia often appears several years before the anemia becomes manifest (Reimann). Thus Schaumann

mentions a case of pain in the tongue for 5 years before the anemia was diagnosed, and of Heyn's 39 patients, 5 had glossitis for over 3 years. Before the introduction of the liver treatment it was frequently observed that the glossitis fluctuated in intensity with the anemia. During liver treatment the glossitis will practically always disappear—always before complete hematological remission is reached, and frequently before the reticulocyte crisis. Thereafter, as long as the treatment is sufficient, the tongue will be natural, but a return of the glossitis will be rather a sure sign that the therapy is insufficient (Oatway and Middleton, Isaacs, Sturgis and Smith). An increased dose will cause the glossitis to disappear once more. Huston alone claims to have observed a case where affection of the tongue remained after full remission had been obtained by means of liver. This tongue however was completely atrophic and smooth on the surface and did not resemble the typical Hunter glossitis.

It is especially after the introduction of the liver treatment that investigations have been pursued regarding the superficial glossitis. It was then found that other diseases besides pernicious anemia could produce similar phenomena.

Long before Hunter, Möller (1851) described some «chronic excoriations» on the tongue in women, most of whom were bothriocephalus carriers. These excoriations looked exactly like the red patches that Hunter described in the case of pernicious anemia. Later several investigators have confirmed the presence of glossitis in patients with bothriocephalus anemia.

A similar affection of the tongue is observed also in the case of other hyperchromic anemias. Thus Larabee, as the first, describes a case of pernicious anemia of pregnancy accompanied by a smooth tongue and red edematous patches.

Far more pronounced, but of another appearance, is the affection of the tongue in the form of anemia which is characterized by the Plummer-Vinson syndrome first described by Plummer 1914, involving dysphagia, hypochromic anemia and glossitis. Later it has been treated by Kelly, Patterson, Vinson, Wills and Waldenström. In all these papers the glossitis is characterized as a pure atrophy of the mucous membrane, and it is described how the tongue, despite the anemia, frequently is strongly red. Like the patients with pernicious anemia, these patients com-

plain of pain in the tongue. Moreover, the Plummer-Vinson patients suffer from dysphagia. In most cases treatment with iron succeeds in mitigating the affection and make the tongue natural again. Most frequently it is a question of iron deficiency — which agrees with the circumstance that typical cases are found without anemia, but with low values of the serum iron.

There is hardly any doubt, however, that the limiting of the Plummer-Vinson syndrome to hypochronic anemia is not sufficiently inclusive. Several authors (Jones and Owen, Witts) describe cases where the anemia that accompanies the dysphagia is hyperchromic, and where the dysphagia disappears with the liver treatment of the anemia. Several other cases of the Plummer-Vinson syndrome are described, where the cause is not iron deficiency, but other deficiency diseases, and then practically always involving an insufficiency of vitamins of the B-group (Jankelson). There seems, however, to be two kinds of avitaminosis, *viz.*, ariboflavinosis and pellagra, which are of special interest in this connection.

When Sebrell and Butler in 1938 first described ariboflavinosis, they paid special attention to the changes of the lips and the skin. According to later description by Sydenstriker and co-workers, and by Lundh and Geill, affection of the tongue may also occur, and then always in the form of a smooth naked tongue. It seems as if a smooth tongue in patients with an avitaminosis must be considered a definite sign of ariboflavinosis.

In pellagra too we find a typical glossitis. In the pure form of pellagra, without other avitaminoses than nicotin amide deficiency, the tongue will be a bright red and edematous »d'un aspect framboise», and only when other deficiency occurs at the same time the tongue will be naked and smooth. (Justin-Besancon and Lwoff.)

In addition to these avitaminoses, where a further analysis is possible, the literature describes numerous cases of glossitis in patients whose diet has been such that there is reason to suspect an avitaminosis as a contributing cause. Thus Keefer describes cases, in China, of hypochromic anemia accompanied by nutritional disturbances of other kind, all with a smooth tongue. One may also mention the cases of glossitis which Akroyd found in India, though it seems most natural to suspect an ariboflavinosis. Moreover, there is the simple glossitis mentioned by Garcia as observed during the Spanish civil war; it appears to resemble the pellagra

glossitis. Within the same category belong in all probability the cases which Degos et al and Beebes describe, of smooth tongue and reduced secretion of the externally secreting glands. It may be presumed that the grouping also should include the gradually increasing number of cases with avitaminoses developing after operation of the intestinal tract.

Frequently, however, it is difficult to evaluate these investigations, especially with respect to the affection of the tongue, since, as a rule, the authors do not give a sufficiently explicit description of the appearance of the tongue.

Besides in the cases of these deficiency diseases the tongue may be completely smooth during the early stages of azotemic uremia (Fishberg), but during later stages a rather heavy coating is more commonly found.

The type of atrophy of the mucous membrane of the tongue observed in patients with idiopathic xerostomia appears to have escaped general notice. The earliest descriptions mention that the tongue as a rule is free from papillae, smoothly glazed or exhibiting a nubbled surface, like a kind of lingua scrotalis (Hutchinson, Fellens).

Among the earliest investigators who dealt with the smooth tongue it was agreed that in by far the most cases this phenomenon was an expression of a reduced gastric secretion. The idea is supported by the fact that it is in the very diseases mentioned above that achylia gastrica is most frequently found. The question has been thoroughly investigated by Arne Faber, whose purpose it was to find out whether it was possible, on the basis of the appearance of the tongue, to diagnose gastric achylia, so that the test meal might be avoided. In all cases where he found an atrophic mucous membrane of the tongue he also found gastric achylia, but the latter was also found in patients with normal tongue. Cobert and Morawitz, who investigated the same question, found only a positive atrophy of the mucous membrane of the tongue in patients with pernicious anemia, while otherwise they found no association with gastric achylia, though by far most of the patients with atrophy of the tongue suffered from this disease. They pointed out, however that the atrophy did not appear until old age, and perhaps should be interpreted as a link in the general senile changes.

What is said here shows that the literature presents a number of reasons for the occurrence of an atrophied mucous membrane of

the tongue. Moreover, the majority of authors are agreed that this affection is found almost exclusively in the old, and first of all in women.

### *Histological Investigation.*

Histological investigations of the smooth tongue all show the same. Thus Wahlgren finds that the epithelium is low, with considerably reduced cornification. The usual cornification of the tips of the papillae is lacking, and is found only between the connective tissue papillae. The latter are, especially in old age, considerably below normal height. In the connective tissue only moderate signs of inflammation are seen. That the connective tissue papillae are lower, but as a rule existing, is also shown *intra vitam* by Henning in microscopy of the tongue. An idea of the amount of cornified tissue that can be found on a tongue may be gained through vital staining with methylene blue (Henning).

The present author has been unable to find any description of the mucous membrane of the tongue as regards the red patches in pernicious anemia.

### *Pathogenesis.*

The pathogenesis of the atrophy of the mucous membrane of the tongue is still unexplained. Waldenström's theory is the first one proposed. He considers the atrophy a sign of a deficiency disease that especially attacks the surface epithelium. Iron deficiency should be the most important factor in this connection, but also deficiency of other substances should give rise to the same symptoms. Other symptoms of the affection should be the red lips, the fissures in the corners of the mouth, the brittle, grooved nails, and achylia gastrica. The theory is tempting, but, as will later be shown, it is hardly adequate.

In an earlier paper (M. Faber 1942) the author has discussed the symptoms in xerostomia and mentioned how frequently this disease is accompanied by a smooth tongue. This has led to the proposal of a working hypothesis to the effect that in all cases a reduced salivary secretion is responsible for the smooth tongue. The idea will now be discussed in detail.

## Own Investigations.

The author's material includes 51 patients, being all patients with complete or partial atrophy of the mucous membrane of the tongue that were observed, during the period of study, at the Medical Policlinic. To these should be added 3 patients with Hunter's glossitis and one with pellagrous glossitis who were examined at the same time or later.

Of the patients 51 showed a complete or partly loss of the papillae on the dorsum of the tongue. This atrophy is very characteristic. In the milder case there is, as a rule, observed symmetrically 1 cm large patches, with no papillae, on the dorsum linguae. On the remainder of the tongue the papillae are generally small, and there is hardly ever observed any coating. In the more severe cases the papillae are lacking over still larger areas of the tongue and in the most severe cases not a single filiform papilla can be observed anywhere. The mucous membrane becomes absolutely smooth, and the tongue may have the appearance of a glazed surface. In such cases the tongue is frequently small, atrophic. In the severe cases, especially those that have lasted for years, the surface is less smooth, having a nubbled appearance. The epithelium is

Table 1.

Diagnosis	Male	Female	Total
Pernicious anemia .....	3	3	6
"    of pregnancy .....	0	3	3
Sideropenic anemia with gastric achylia .....	0	7	7
"    without " .....	0	2	2
Syndroma Plummer-Vinson .....	2	2	4
Gastric achylia without anemia .....	0	10	10
Cancer ventriculi .....	0	1	1
Sprue, non-tropical .....	0	1	1
Ariboflavinosis .....	1	2	3
Diabetes mellitus .....	0	2	2
Stomatitis aphthosa .....	0	1	1
Sialoadenitis chronica (primary) .....	1	3	4
Xerostomia kryptogenica without gastric achylia	3	4	7
Total	10	41	51

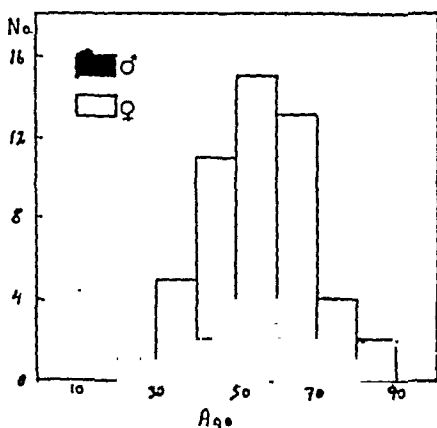


Fig. 1.

then so dry and smooth that wrinkles appear when one presses on it with a spatula. In the milder cases the tongue is usually of a normal colour, but in the severe ones it is a bright red, even if the patient at the same time suffers from a rather pronounced anemia. The explanation must be that in these severe cases the mucous membrane is extremely thin. In the severe cases the internal mucous membrane of the cheeks looks just like the mucous membrane of the tongue—it is bright red and «glazed».

The investigation also includes 4 cases of Hunter's glossitis, *i. e.*, with red patches on the tip of the tongue and along the margin, with edematous papillae in the red parts of the tongue, and with rather pronounced pains in the tongue. One of these patients also showed atrophy of the papillae on dorsum linguae. One other case deserves special mention, *viz.*, that of a patient with a bright red tongue without coating, edematous, and somewhat smoothed off. The patient also suffered from severe glossodynia. The case was diagnosed as monosymptomatic pellagra.

Table 1 gives a review of the diagnoses for the patients with atrophy of the mucous membrane. It will be seen that the material includes nearly all the diseases which according to the literature are responsible for the smooth tongue. Hence there should be no reason for going into the details of these diagnoses. Attention, however, is called to the relatively large number of patients with chronic sialoadenitis. The table also includes 6 cases of pernicious anemia. In these cases the tongue was smooth; only in one case

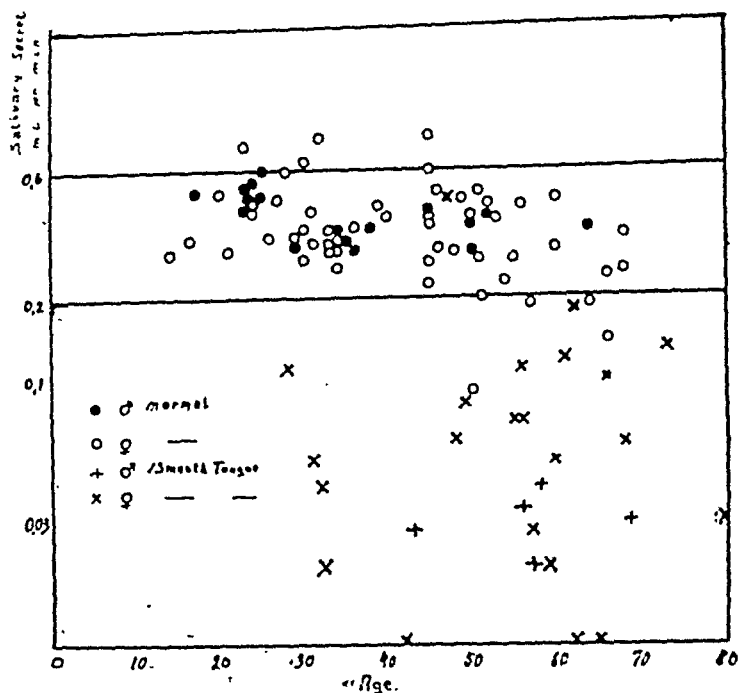


Fig. 2.

the typical Hunter glossitis too was encountered. Fig. 1 also shows the distribution by age. It will be seen that the middle-aged predominate. This distribution is probably much influenced by the age distribution of the patients consulting the Polyclinic, a much greater number being expected from the higher age classes. The figure also shows the distribution by sex. As expected, most of the patients are women, only 10 being men.

If we now turn to the question of the cause of this atrophy of the mucous membrane of the tongue we find, as mentioned above, no satisfactory answer in the literature. Waldenström's theory is inadequate. Thus it makes no attempt to differentiate between the purely atrophic mucous membrane and the more localized forms of glossitis which are found in pernicious anemia. Moreover, it cannot explain the forms of atrophy which are found in patients who show no sign of any deficiency disease. Nor can Waldenström's theory account for the smooth tongue observed in infants during the first few weeks.

In some cases the explanation is quite simple. Thus the present material includes a patient with a partly atrophic mucous mem-



brane of the tongue where the atrophy must be considered due to an aphthous stomatitis that has persisted for years. The recurring aphthae have in this case led to a destruction of the mucous membrane, so that papillae are no longer formed when the aphthae are healed. The same mechanism is seen, *e. g.*, in the case of large corruptions.

The other patients with atrophy of the mucous membrane may be grouped together, if we apply another point of view. It has been mentioned that a smooth tongue frequently is observed in severe xerostomia — it would therefore seem natural to measure the salivary secretion in all cases of smooth tongue. At first this was done simply by placing a lump of sugar under the tongue and measuring the time it took for the sugar to dissolve. Later the saliva has been collected quantitatively (M. Faber). The cases where the saliva has been collected are included in fig. 2, together with the results from a normal material selected among patients who did not have any disease which, according to experience, reduces the salivary secretion. The figure shows that practically all patients with atrophy of the mucous membrane have reduced salivary secretion below the lower border of the normal. The only exception is the above mentioned patient with aphthous stomatitis. We find practically the same picture in the case of the patients who have only been subjected to the sugar test.

The salivary reduction in these case has, as the figure shows, been extremely pronounced. Thus it seems that in these patients with atrophy of the mucous membrane of the tongue one may always expect a reduced salivary secretion. Hence it should be reasonable to assume that it is this reduction of the moisture on the mucous membrane that is the direct cause of the atrophy.

That changes may occur in the surface epithelium when the secretion from the glands that moisten a mucous membrane becomes too low is well known from observations in connection with conjunctiva and cornea. Here it is demonstrated by Sjögren that the filiform keratitis almost exclusively is found in patients with reduced lacrymal secretion, and that it occurs unilaterally when a lacrymal gland is removed. It may be mentioned, moreover, that in patients with reduced vaginal secretion there can be seen a change of the vaginal epithelia resembling that of the mucous membrane of the mouth.

The case of the infant is of interest. At birth the tongue has a slight coating which again disappears during the first ten days. During the next 2 to 3 weeks the infant's tongue is smooth and a bright red, like the mucous membrane of the mouth, and does not look much different from the atrophic mucous membrane in adults. During the same time the mouth is dry, without saliva, and it is during this period that the children are most troubled by thrush. At the age of 2 to 3 weeks there suddenly appears a fine white coating, at the same time as the salivary glands begin to show increased secretion and the child salivates. That the child is born with a coating of the tongue is probably due to the circumstance that in the uterus it has had sufficient moistening of the mouth cavity from liquor amnii.

It is only in infants and adults of advanced age that the tongue becomes completely smooth when the salivary secretion falls. That the phenomenon is found in infants is undoubtedly due to the circumstance that the connective tissue papillae which form the basis for the cornification as yet are so small. In old age these papillae have decreased in size, as shown, for example, by Wahlgren. In the intervening years it is rare to find absolutely smooth tongues. In the very young one observes a distinct decrease in the coating of the tongue. In the somewhat older there is observed a partial atrophy, localized to the middle of dorsum linguae, and not until the higher ages do we find the total atrophy as the most frequent form. Often the impression is that the mucous membrane of the tongue in older people may be prepared, so that a relatively small change in salivary secretion rapidly may lead to a smooth tongue. Thus the author in two cases has observed cerebral thrombosis accompanied by a reduction of the salivary secretion, which in the course of less than 24 hours resulted in a previously normal mucous membrane of the tongue becoming smooth and of a bright red colour; later, when the secretion again increased, the mucous membrane assumed its normal appearance. Moreover, there is no doubt that the degree of dryness which is found in the mouth is of considerable importance. The author has had the opportunity through several years to observe a boy, now 15 years of age, who suffers from a congenital aplasia of the salivary glands. When first examined, the mucous membrane was not definitely pathological, showing variations between a strong coating and a naked tongue

with small papillae. When last seen the tongue was nubbled and covered with a fine thin epithelium, but without the slightest trace of papillae. The secretion was now so poor that not even the work of mastication could produce any saliva. If that had been the case the atrophy would probably never have advanced so far.

In the introduction it was mentioned that it has been tried, at least with some justification, to associate the smooth tongue with achylia gastrica. The idea seems natural when considering the reduced salivary secretion as responsible for the atrophy of the mucous membrane. In an earlier paper the author has shown that there is an intimate relationship between a reduced salivary secretion and a reduced gastric secretion (M. Faber), and that this observation might be extended to apply to a universal sicca syndrome comprising most of the externally secreting glands (Degos and co-workers, Beebe) — a syndrome which in adults often has the appearance of a pronounced Plummer-Vinson syndrome. Thus it is not surprising that the patient with achylia gastrica so frequently has a smooth tongue. On the other hand, since the reduction of the secretion does not necessarily run parallel in the two glandular systems, it is quite natural too that the smooth tongue is not invariably found in cases of achylia gastrica.

While the smooth atrophic tongue thus may be explained on the basis of a reduced salivary secretion, the situation is different in the case of the typical Hunter's glossitis. As already mentioned, the author has made investigations of the salivary secretion in 4 patients with this affection in connection with untreated pernicious anemia. The salivary secretion of the patients is recorded in table 2. It will be seen that one patient, who also has a smooth tongue,

Table 2.

No	Sex	Age	Diagnosis	Hgbl %	R.B.C.	Index col.	Salivary secretion at rest ml. pr. min.
1	M	63	Pernicious anemia	55	2.06	1.22	0.38
2	M	34	»	104	4.75	1.00	0.45
3	K	69	»	50	1.76	1.40	0.32
4	M	61	»	75	2.69	1.30	0.007
5	M	38	Pellagra	98	4.70	1.03	1.82

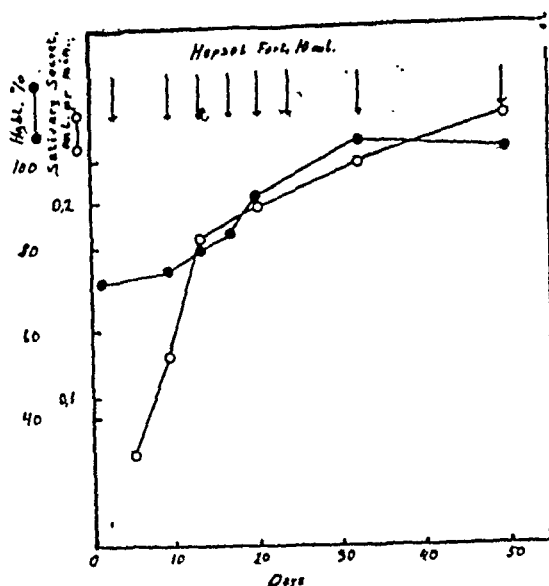


Fig. 3.

shows reduced salivary secretion, while the three others show normal secretion. The same table shows the salivary secretion in a patient with an affection of the tongue which is considered a case of monosymptomatic pellagra. His salivary secretion shows an increase, so that the basal secretion is as strong as after stimulation with pilocarpine. After treatment with liver extract the secretion falls in the course of 2 days to normal values, at the same time as the alterations of the tongue disappear. Further data on such cases are desirable.

According to these few orienting investigations the isolated Hunter's glossitis must be considered an affection entirely different from what we call the smooth tongue. In support one may cite the extremely short life of the affection, patches frequently appearing one day and being gone the next, even if no treatment is given. At any rate, they disappear promptly upon liver treatment. It is quite otherwise with the smooth mucous membrane when encountered in patients with pernicious anemia. Fig. 3 shows how the salivary secretion slowly rises during the liver treatment, and not until it has reached the low normal value of 0.2 ml pr minute is the atrophy seen to disappear after 14 days of treatment. The Hunter glossitis on the other hand disappeared 2 days after the first liver

treatment. If the reduced salivary secretion lasts for a longer period of time there may develop, secondarily, a chronic inflammation of the salivary glands with the result that the atrophy of the mucous membrane becomes permanent. This is the phenomenon that Huston has observed, and the present author has seen a somewhat similar case in a woman where, notwithstanding liver and ventricular preparations and complete hæmatological remission, the tongue remained perfectly smooth. This patient had a salivary secretion of only 0.008 ml per minute.

### Summary.

On basis of the literature a review is given of the diseases in which an affection of the tongue may be expected. It is concluded that one must differentiate between — on the one hand — a smooth atrophic mucous membrane of the tongue, as seen, for example, in iron deficiency anemia, ariboflavinosis, gastric achylia, and sometimes in pernicious anemia, and — on the other hand — the affection of the tongue which is found in other patients with pernicious anemia, and which in its classical form is described by Müller and Hunter. A third type of glossitis is observed in pellagra.

Examination of 51 patients with smooth atrophic tongue shows that the salivary secretion is always reduced, except in the rare case of a local cause like aphtous stomatitis. This fact is in contrast to what is found in other types of glossitis where the salivary secretion is normal or increased. It is shown that the reduction of the salivary secretion (with the exception mentioned) is found in all forms of smooth tongue, and that the mucous membrane of the tongue again becomes normal when the secretion rises to normal values. On the basis of these and various other observations it is concluded that the atrophy of the mucous membrane must be due to the xerostomia.

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From the Medical Clinic A of the University of Copenhagen, the Rigs-hospital, (Chief: Professor Carl Sonne, M. D.) and from the Medical Department of the Militærhospital, Copenhagen (Chief: Chr. N. J. Gram, M. D.).

## Studies on the effort syndrome.

### I. The Patients' Capacity for Work and the Variations in the Arterial Pressures and Pulse Rate During Muscular Work Compared with the Conditions Found in Normals.<sup>1</sup>

By

B. CHR. CHRISTENSEN, M. D.

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### The effort syndrome.

The carrying out of great muscular works will always provoke symptoms from the circulatory and the respiratory organs. The promptness with which these symptoms are provoked varies from one individual to the other dependent on constitution, training etc., and also within one individual dependent on tiredness and working conditions. There is practically a smooth transition from the response to muscular work of the normal, well-trained organism to the response of the invalid. However, there is found a rather well defined group of persons in whom even slight muscular exertions provoke various symptoms, which have been regarded as signs of an insufficiency of the circulation, though a thorough general medical and a special cardiological examination afford no basis for an organic affection, especially not of the lungs and the heart. The most frequently occurring symptoms in these persons are dyspnea, palpitations, precordial sensations, fatigue, giddiness, tremulousness, and in pronounced cases fainting fits.

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<sup>1</sup> The investigations have been carried out with financial support from the Kong Christian den Tiende's Fund and from Miss P. A. Brandt's Scholarship.

*Nomenclature and History.*

The abnormal response to work was first described by Harts-horne (1864) under the term »Muscular Exhaustion of the Heart» in a work on cardiac affections in the American army during the Civil War. He is of the view that the symptoms are due to overstrain of the heart.

Some years later DaCosta (1871) gave an exhaustive account of the affection, called by him »Irritable Heart». On the basis of 200 cases a detailed description is given of the symptomatology of the affection, to which later writers have had nothing of importance to add. DaCosta says expressly that the affection may also be observed in other persons than soldiers.

About the same time the affection was mentioned by Arthur B.R. Myers (1875), who observed it in the British soldiers in India.

As already pointed out by DaCosta this affection is found both among civilians and among soldiers. As, however, the symptoms are provoked by bodily exertions it is quite natural that it should be mainly army physicians who occupy themselves with the affection, and that this affection is in a particular degree made an object of investigation during wartime, when many in part untrained individuals are exposed to great bodily exertions.

During the War of 1914—18 especially Thomas Lewis and collaborators bestowed much labour on finding the cause of the abnormal response to work in, to all appearance, normal individuals. During the War the British official military term of the affection was »Disordered Action of the Heart», abbreviated to »D.A.H.».

In Thomas Lewis' and his collaborators' first report on the affection (Meakins, Lewis, and others, 1916) they used DaCosta's term »Irritable Heart».

At a later stage of this investigations Lewis introduced the term »Effort Syndrome» for this pathological picture, and he defined it as follows (1919), »When I use the term »effort syndrome» I have in mind the symptoms and signs which follow exercise in health; but I believe that I recognise the same or a very similar group of symptoms in a large class of patients in ill-health. In patients of this class, if no signs of disease are anywhere discovered, I say that they suffer from the »effort syndrome». The difference in



symptomatology which exists between health and this form of ill-health is largely a difference in degree; the gauge is the amount of work which, performed in a given space of time, will provoke the symptoms».

The American investigators who during the War collaborated with Lewis were not content with the term »effort syndrome», for which reason they proposed the name of »neurocirculatory asthenia». Paul D. White, (Craig & White 1934) pointed out, in contrast with Lewis, that there is a qualitative difference between the response to work of the patients mentioned here and that of the normals, for which reason they preferred the term »neurocirculatory asthenia» to »effort syndrome».

The German writers occupying themselves with the same subject are of opinion that the underlying affection is a neurosis, as appears plainly from their nomenclature, thus for instance Aschenheim (1915) termed the syndrome »neurosis cordis».

### *Etiology.*

Some writers (Aschenheim (1915), Farlane (1918), Bainbridge (1919), Barlow (1920), Kerley (1920), and Rotschild (1930) point out the universal or contingently cardiovascular constitutional weakness as the main cause.

Others attach the greatest importance to a previous latent or manifest infection (DaCosta (1871), J. Parkinson (1916), Friedlander & Freyhof (1918), Trotter (1918), and Farlane (1918)).

Craig & White (1934) have found, however, on an analysis of 100 cases of the effort syndrome among civilians, that past infections play but an insignificant part in proportion to the psychoneuroses.

It has also been maintained that the cause should be a hyperthyreosis (Barr (1916), Stoney (1916), C. P. White & Hernaman-Johnson (1916), and Brooks (1918)).

The significance of preceding bodily overstrain for the occurrence of the syndrome has been emphasized by Hartshorne (1864), Grober (1914), Kraus (1915), Fürbringer (1915), and finally by Münter (1915), who adds that the cause that young people cannot endure bodily exertion is »der gewaltigen Schädigungen des Kultur- und Zivilisationslebens unserer Zeit».

Gradually, however, the view has become prevalent that in the majority of the cases it is a psychoneurosis that causes the different symptoms (Graul (1915), Schott (1915), Abrahams (1917), Robey & Boas (1918), Oppenheimer & Rothschild (1918), Musser (1919), Culpin (1920), Fraser (1940), and Spillane (1940)).

It is to be presumed that habits of life, occupation, etc. are of significance at the occurrence of the syndrome, and it appears from Lewis' statement (1918) that about half of the affected soldiers had before the call-out been engaged in sedentary work and had never done any kind of sporting. As to the habits of life it cannot be decided with certainty whether they are capable of bringing about the syndrome, or whether they are caused by the syndrome.

By way of summing up it may be said that all existing or past physical and mental affections together with prolonged bodily overstrain reduce the physical capacity for work of the individuals in question so that they tire rather quickly. But the cases of abnormally prompt exhaustion in which the underlying affection is known ought not, however, to be included under the term of effort syndrome, which should be applied exclusively of the cases with typical symptoms from exertion in apparently perfectly normal persons.

### *Pathogenesis.*

Haldane, Meakins, & Priestley (1918—19) suppose the cause of the syndrome to be «shallow breathing». This is considered to induce anoxemia, which should provoke the different symptoms.

Sonne (1923) mentions the possibility that the patients hyperventilate, thereby releasing carbon dioxide so that an acapnia is developed, and he calls attention to the fact that the symptoms of the effort syndrome are typical acapnial symptoms.

Kerr, Dalton, & Glicke (1937) and Sargant (1940) consider it possible, on the basis of examinations of nervous apprehensive patients, to set up the following pathogenetic development: anxiety — hyperventilation — alkalosis, etc.

Soley & Shock (1938) and Guttman & Jones (1940) have made experiments of hyperventilation on patients with the effort syndrome; but only in 50 per cent they succeeded in provoking typical

symptoms, so accordingly they are of opinion that the hyper-ventilation cannot be the only cause of the effort syndrome.

However, the investigations mentioned here into the pathogenesis of the effort syndrome all have the disadvantage of having been undertaken at rest and not under such conditions as generally provoke the typical symptoms. As far as is known no investigations have been made of these patients *during* muscular work. Not till such investigations are undertaken there will be a possibility of getting information on the pathogenesis of the affection. The investigations in hand of patients at rest are indicative that hyper-ventilation may induce the symptoms in question.

### *Occurrence.*

In order to get an impression of the frequency of the affection P. D. White & Jones (1928) have studied the final diagnoses of 3000 patients who consulted a doctor or were admitted into hospital on account of cardiac symptoms. It appears from this investigation that 302 or 10 per cent were suffering from the effort syndrome.

Craig & White (1934) have investigated 100 cases of the effort syndrome observed in an ordinary mixed civilian practice. It appears from these investigations that the females have a slight majority (69 per cent). Among the 100 cases ages from 12 to 69 are found represented, the average age being 36.

### *Symptoms.*

A comparison between Lewis' (1918) and Craig & White's (1934) works show that the prevailing symptoms are the same in those liable to military service and the civilians, as also appears from a work by Neuhof (1919).

The four cardinal symptoms are palpitations, a feeling of air hunger (shortness of breath), precordial sensations, together with a feeling of exhaustion. All these symptoms are provoked by light or moderately hard work.

Moreover giddiness, fainting headache and tremulousness during and after exertion, nervousness and insomnia are mentioned as frequently occurring symptoms.

*Physical Findings.*

On the ordinary physical examination of the patient at rest nothing abnormal is observed. There is no connection between build of body and effort syndrome. The stethoscopy of the heart presents no characteristic peculiarities. The pulse frequency at rest is in some cases higher than in normals.

By orthodiagraphic measurements (Meakins & Gunson, 1918) and electrocardiographic examinations (J. Parkinson, 1917 (a) and Th. Lewis, 1918) made both at rest and after exertion presented no characteristic changes.

Paul D. White & Hahn (1929) call attention to the fact that in patients with the effort syndrome a few deep inspirations (sighs) are often observed both at rest and during bodily work. Christie (1935) has observed, by a review of spirometer curves from patients suffering from the effort syndrome, that the midcapacity is not constant, and that the respiratory excursions are not equal and the respiration rate not regular. In this connection he calls attention to the fact that the changes mentioned here are rare in normals and never so pronounced as in the patients. These observations must be seen in connection with the phenomenon, to which especially Kerr, Dalton, & Gliebe (1937) have drawn attention, that, unlike normals, the apprehensive and nervous patients have a very irregular respiration.

Levine & Wilson (1919) have examined about the vital capacity of 131 patients and found that only in a few cases it was slightly reduced. Adams & Sturgis (1919) arrived at the same result after having examined 180 patients. These latter writers examined at the same time the contents of carbon dioxide in venous blood at rest on 45 patients and found normal values.

Drury (1920) has examined about the contents of carbon dioxide in the alveolar air of these patients by means of the Haldane-Priestley method and found low but normal values at rest, and besides that the lowest values are found in the patients presenting the most pronounced symptoms. On examinations after bodily exertion the values were likewise found to be lower than in normals.

Blood pressure and pulse rate after graded work have been examined by Cotton, Rapport, & Lewis (1917, a) and by Meakins

& Gunson (1917, a). It appears from these examinations that the patients present a greater rise in blood pressure and pulse rate after the discontinuation of the work and a slower return to the resting values than normals. Lewis emphasizes that the differences are only quantitative.

This review of symptoms and physical examinations indicates that when the patient is at rest there has been demonstrated something abnormal on two points, i.e. White's and Christie's demonstration of changed respiration and Drury's demonstration of low carbon dioxide partial pressures in the alveolar air.

### *Treatment.*

From the examinations made by Lewis and his collaborators (Lewis' report, 1918) it appears that confinement to bed aggravates the symptoms. The only treatment that has proved favourable is graded physical training, as indicated by Lewis. By this treatment about 50 per cent improve or get cured, whereas the other half are unaffected being still unfit for bodily work. Further it appears from his report that the previous civilian occupation is of no significance for the result of the treatment.

### *Prognosis.*

There are found no statements dealing with the prognosis of the affection as regards the civilian patients and only a single report in the case of the military patients. By the nature of the case this report gives information only of a single group of the patients suffering from the effort syndrome.

Grant (1926) has by annual inquiries and examinations through 5 years studied the course in 665 patients living in London, who had been discharged from military hospitals with the diagnosis of effort syndrome. It appears from the examinations that the mortality rate among patients is the same as among normals of the same sex and age. 15.3 per cent recovered completely, 17.8 per cent improved, 56.2 per cent remained stationary, and 3.2 per cent showed exacerbation. The rest developed other diseases during the examination period (tuberculosis in 22 cases, which according to Grant's calculation should be double the number of cases in normals of the same ageclass) or died. There was found no preponderance of organic cardiac affections.

### Author's Methodics.

As appears from the above nothing certain is known as to the pathogenesis of the effort syndrome. This is among others due to the fact that no systematic examinations have been undertaken so far of patients with this affection *during* muscular work. Lewis has not proved the rightness of the hypothesis that there should be a smooth transition from the response to exertion of the normals to that of the patients. Nor has White, who unlike Lewis is of opinion that there is a qualitative difference between the response of the normals and that of the patients, proved the truth of his theory.

The object of the investigations described here has therefore been partly to determine the maximal capacity for bodily work of the patients and partly to determine the variations in blood pressures and pulse rate during the work and compare these values with corresponding values from normal persons of the same sex and age-class, in order to make out whether there is any essential difference in the response to exertion of the 2 groups.

The previous investigations into the blood pressure variations in normals during muscular work have shown that both systolic and diastolic blood pressures rise immediately at the beginning of the work to certain values which remain rather unchanged if the work requires moderate effort. At great and exhausting works there is often seen a constant rise in the blood pressure during the whole working period (Moritz, 1903). In elderly people and very occasionally at very fatiguing work there has been observed a fall in the blood pressure during the muscular work itself (Grebner & Grünbaum, (1899), Masing (1902)).

Oscillometric blood pressure measurements with Pachon's oscillometer have been made by Bergman (1922).

Eldahl (1933, b) has made a number of measurements during hard muscular work on Krogh's bicycleergometer by means of an optically registering oscillograph constructed by himself. He has found that the systolic pressure increases considerably more than the diastolic pressure, which at a work of 1760 kgm per minute increases only from 100 to 135 mm Hg, whereas the systolic pressure increases from 140 to 240 mm Hg.

Em. Hansen (1937) has likewise made oscillographic measur-

ements on normal persons during muscular work and found the same variations as Eldahl (1933, b).

On the examination technique rendered here the following requirements were made:

- 1) All the persons examined should have about the same training in carrying out the muscular work in question.
- 2) The muscular work should be easy to grade and easy to reproduce.
- 3) Determinations of the blood pressure should be made several times during the work itself.

Krogh's bicycleergometer gives the best working conditions for laboratory investigations, and at the same time there is the advantage of applying it that all young people are in advance more or less trained in bicycling.

For the determination of the blood pressures the oscillometric method was applied, because it may easily be made optically registering, and because the shape of the oscillometric curve gives information on the state of contraction of the artery measured on.

A further account of the theory of the oscillometric curve has been given a.o. by J. Plesch (1935) and the author (9). Accordingly it shall only be mentioned that in the description of the author's investigations 2 oscillometric criteria will be applied, viz. the occurrence of the first proper oscillation at a pressure that will be called the 1st pressure, and the occurrence of the maximal or last maximal oscillation at a pressure that will be called the 2nd pressure.

The 1st and the 2nd pressures lie about 5 mm. higher than the auscultatorily determined systolic and diastolic pressures (Dan Prytz, 1942).

The oscillograph applied for these investigations is the one constructed by Eldahl (1933, a), described in a previous work of the author (9). It is used together with the double cuff indicated by Gallavardin (1922) and is constructed so as to register only the volume oscillations in the distal cuff.

## Examinations of Normal Persons During Muscular Work.

All the experiments were made in the middle of the day about 1 hour after lunch, after the person experimented on had been keeping quiet in the laboratory for about half an hour. After this half hour's rest he mounted the bicycleergometer, where he sat quiet for at least 10 minutes before the working experiment was begun. During the resting period on the bicycle 1 or 2 determinations of blood pressure and pulse rate were made. The last determination was made immediately before the beginning of the work. During the work itself, lasting for 30 minutes, or in the case of the great weights as long as the person was able to ride, there were made on an average 4 to 6 measurements.

The examinations comprise 50 working experiments on 8 normal persons carrying out from 300 kilogrammeter (kgm) to 1200 kgm per minute for up to 30 minutes. Many of the persons could have carried out still greater amounts of work, for instance from 1350 kgm to 1500 kgm per minute. But at such great amounts of work it proved impossible to make a serviceable oscillometric measurement, for which reason works exceeding 1200 kgm per minute will be left out of account here. In all cases there was applied a turning speed of the pedals on the bicycleergometer of 50 per minute.

These experiments showed that both the 1st and the 2nd pressures rise to a certain level in the course of the first 2 to 5 working minutes, and that the pressures after that remain rather unchanged during the whole working period. The 1st pressure rises relatively more than the 2nd. There was observed no fall in the blood pressure during the work, not even in the case of the works requiring great effort. Thus the experiments showed the same variations in the arterial pressure during muscular work as found by the writers mentioned in the preceding.

At the works requiring moderate exertion (300 to 600 kgm per minute) the pulse rate rose quickly to a certain level, where it remained unchanged during the whole work. At the greater amounts of work it was observed that the pulse rate rose quickly at first and then more slowly to the working level, which was not reached till after 10 to 20 minutes of work. A few times, at very great and straining works, the pulse rate rose during the



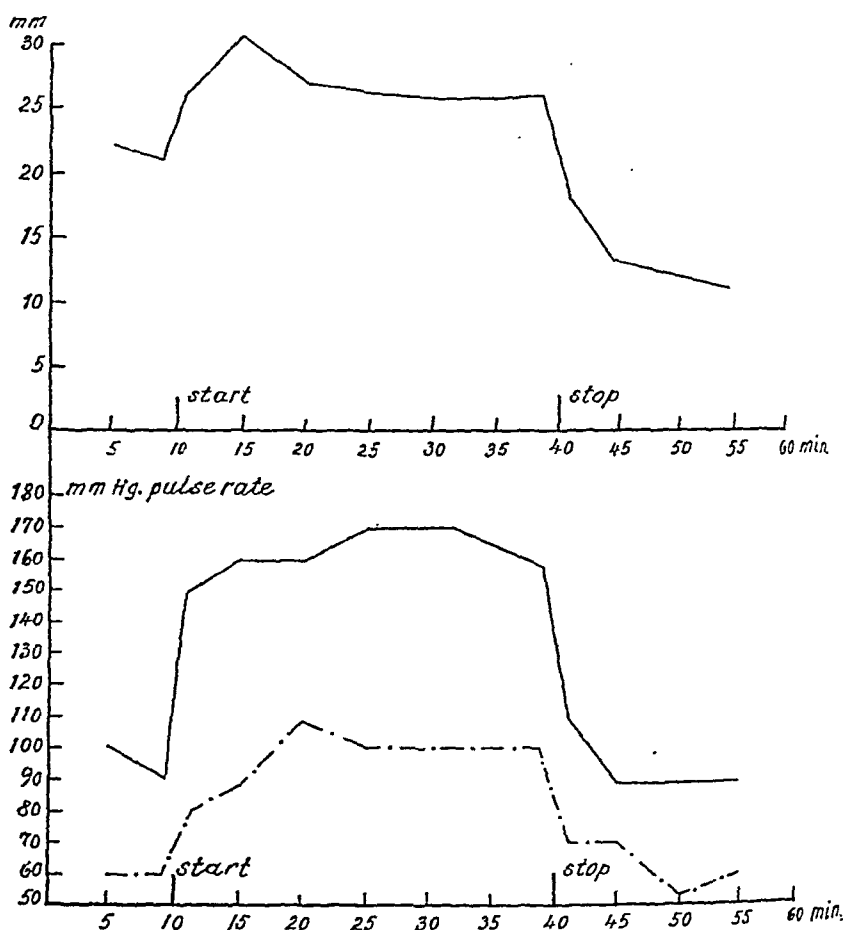


Fig. 1. The variations in the arterial pressures and the range of the maximal oscillation in experiment No. 143. The unbroken line indicates the 1st pressure, —. —. the 2nd pressure. The abscissa indicates the time in minutes. The ordinate: Lower section = the values of the arterial pressures, upper section = the variations in the range of the maximal oscillation expressed in mm.

whole work. The variations in the pulse rate during muscular work demonstrated here coincide perfectly with the results obtained by Hohwü Christensen (1931).

Experiments Nos. 143 and 75 serve as examples of the variations in the arterial pressures and in the pulse rate. In these experiments the work amounted to 900 and 1200 kgm per minute respectively for 30 minutes. The variations in pressures, pulse rate, and range of the maximal oscillations during work are illustrated in figs. 1 and 2. It appears from these illustrations that the arterial pressu-

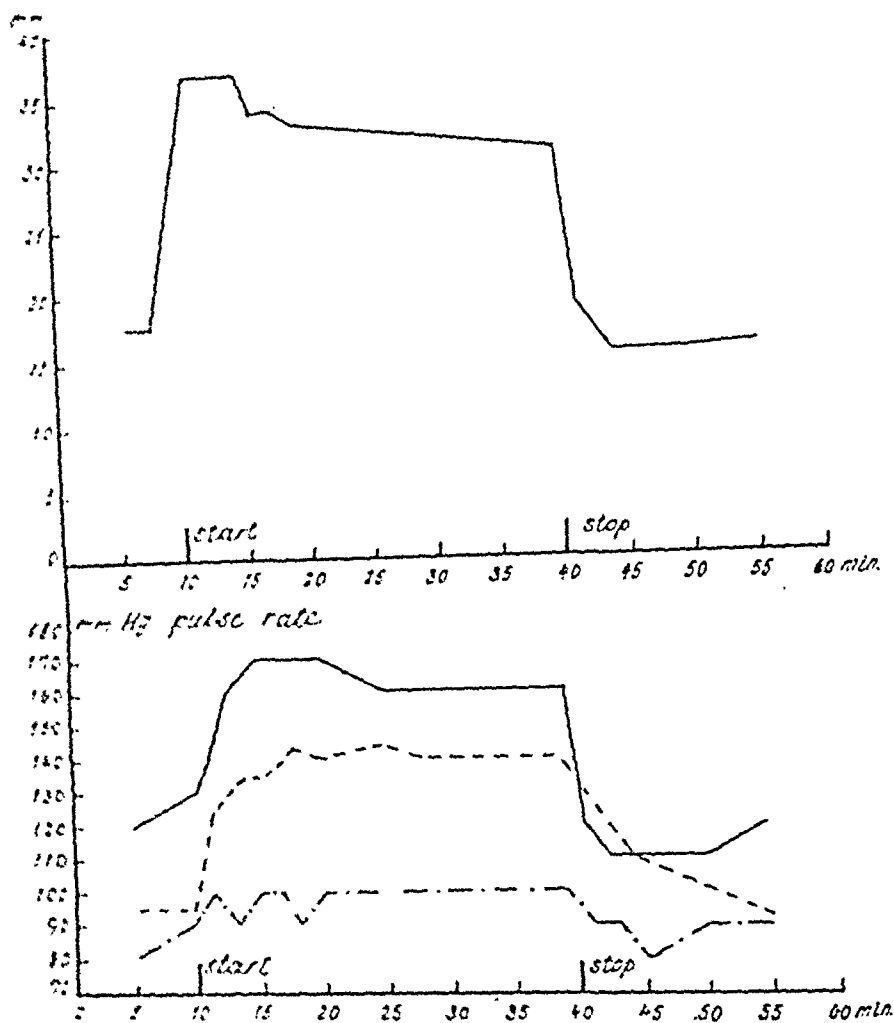


FIG. 2. The variations in the arterial pressures, the pulse rate, and the range of the maximal oscillation in experiment No. 75. Uninterrupted line indicates the 1st pressure, - - - - the 2nd pressure, and — — — — the pulse rate. The ordinate indicates the time in minutes. The ordinate: Lower section = the values of the arterial pressures and the pulse rate. Upper section = the variations in the range of the maximal oscillation expressed in mm.

res, the pulse rate, and the maximal oscillation adjust themselves to the working values in the course of 5 to 10 minutes.

In nearly all the experiments the arterial pressures and the pulse rate reached a steady state in the course of a shorter or longer time dependent on the amount of work. The values measured at this state must be regarded as the response of the person experimented on to the given weight.

Table 1.

The average values of the arterial pressures and the pulse rate at rest and during the different works. 8 normal persons.

Person No.	Work	Number of exper.	1st pressure	2nd pressure	Pulse rate
No. 1. ....	rest	4	114	80	87
	300 kgm.	1	128	94	95
	600 »	1	143	85	113
	900 »	1	146	92	139
	1200 »	1	163	100	143
No. 2. ....	rest	4	107	75	89
	300 kgm.	2	120	81	102
	600 »	1	135	77	133
	1200 »	1	175	103	173
No. 3. ....	rest	7	114	77	99
	300 kgm.	1	130	75	112
	600 »	2	141	83	138
	900 »	3	157	97	167
	1200 »	1	160	120	165
No. 4. ....	rest	7	115	81	95
	300 kgm.	1	145	90	99
	600 »	2	145	93	129
	900 »	3	167	108	166
	1200 »	2	180	120	178
No. 5. ....	rest	6	104	68	78
	300 kgm.	2	135	84	112
	600 »	1	135	86	155
	900 »	2	159	100	?
	1200 »	1	157	95	?
No. 6. ....	rest	7	114	84	98
	300 kgm.	2	126	92	110
	600 »	2	142	87	141
	900 »	3	148	97	161
No 7. ....	rest	4	105	75	76
	600 kgm.	2	157	99	146
	900 »	2	157	105	168
No. 8. ....	rest	9	113	76	82
	300 kgm.	2	128	80	101
	600 »	2	138	83	125
	900 »	3	156	95	159
	1200 »	2	174	101	184

Table 2.

The average resting and working values for the total number of examined normal persons.

Work performed	1st pressure	2nd pressure	Pulse rate
rest	111	77	89
300 kgm.	130	87	105
600 »	142	87	135
900 »	156	100	159
1200	168	106	172

The average figures for each experiment of the values measured at the steady state show that the values obtained by double experiments accord well with each other.

Table 1 renders for each person the average values of the functions mentioned here at rest and during the different works. A comparison of the values in the various persons shows that there is but a slight individual variation. For instance at a work of 900 kgm per minute the 1st pressure varies from 146 mm to 167 mm, the 2nd pressure from 92 mm to 105 mm, and the pulse rate from 139 to 167. Hence average figures have been calculated of resting values and working values for the different works for the total number of persons experimented on. The resulting figures are found in table 2 and will later be used for a comparison with the values from patients with the effort syndrome. It appears from the figures that the 1st pressure rises relatively more than the 2nd pressure at the increasing weights, a fact which has already previously been pointed out by Eldahl (1933, b) and Em. Hansen (1937).

### Examinations During Muscular Work of Patients Suffering from the Effort Syndrome.

8 young men between the ages of 20 and 25 were submitted to examination. Some of the patients had displayed symptoms of the effort syndrome ever since the age of puberty, whereas others did not develop the symptoms till the beginning of the military service. In all cases the symptoms had appeared without a

preceding infection or overstrain, and on a thorough physical examination there were found no facts indicating effects of or the presence of physical disease. None of the patients presented signs of a psychoneurosis. Further it should be mentioned that all types of body stature were represented among the patients.

Neither X-ray examinations of the lungs and the heart, electrocardiography, standard metabolic rate, nor blood examination showed anything abnormal.

Thus neither anamnestically nor on the physical examination it was possible to find anything that could with certainty be regarded as the cause of the syndrome.

All the patients were soldiers admitted with discharge in view, for which reason no great importance had been attached to their possible complaints during work, as these complaints might have been tinged by a desire to continue the service or to obtain discharge.

The general complaints of the patients were shortness of breath, precordial sensations, palpitations, and pronounced fatigue at work of 600 to 900 kgm per minute. A few of the patients complained also of headache and giddiness during work. Besides it was observed that the patients perspired far more than the normals.

The examinations comprise 53 working experiments, at which there were carried out works of from 300 to 1200 kgm per minute for up to 30 minutes. In all cases the turning speed of the pedal of the bicycleergometer was 50 per minute.

It appeared that all the patients could carry out 900 kgm per minute for up to 30 minutes when encouraged to it, and that a few patients could even perform 1200 kgm per minute for up to 18 minutes in spite of the various disagreeable sensations during the work. In this connection it should be born in mind that a work of 900 kgm per minute requires about 8 times as much oxygen as the resting requirement, and that 1200 kgm per minute increases the metabolic rate about 10 times and generally requires a minute volume that is about 8 times as great as the minute volume at rest. Thus the patients in question cannot be said to be asthenic.

The variation in the arterial pressures followed in the main the same course as in the normals, i.e. both the 1st and the 2nd pressures rose in the course of the first 2 to 5 working minutes to a certain level, where it remained during the entire working period. The patients did not either present a constant rise in the blood pressure.

during the whole working period, nor was there in any of them observed a fall in the blood pressure during the work.

The pulse rate showed more often than in normals a prolonged rise during the working period not reaching a steady state till rather late. The rise in the pulse rate was even quite often seen to continue during the whole work. This course of the variations in the pulse rate correspond to the one observed by Hohwü Christensen (1931), who declares that the pulse rate does not reach a steady state at the works that are exhausting for the person experimented on.

Experiment No. 97 with patient No. 5, 600 kgm per minute for 30 minutes, affords an example of the conditions during a muscular work that did not tire the patient in question. The variations in the different functions during work are indicated in fig. 3.

It is seen that the pressures and the pulse rate rose immediately at the beginning of the work to the working level, where they remained unchanged throughout the working period. The range of the oscillations, which at the beginning of the work was greatly increased, decreased during the whole experiment.

Experiment No. 85, in which patient No. 3 carried out 1200 kgm per minute for 11 minutes, serves as an example of the conditions at an exhausting work. The variations in the functions at this great work are indicated in fig. 4. It is seen here that the arterial pressures in all great essentials acted in the same manner as at the above-mentioned experiments. The pulse rate rose constantly throughout the working period. The range of the oscillations, which immediately at the beginning of the work was greatly increased, decreased during the whole work.

These working experiments show that there is no essential differences between the variations in the arterial pressures and the pulse rate of the normals and those of the patients suffering from the effort syndrome. Only the variations which in normals are observed at great fatiguing works are in the patients seen at smaller, often not fatiguing works. This fact bears out Lewis' hypothesis that the phenomena of fatigue observed in these patients are in themselves normal, only they are brought about by a smaller amount of work.

The arterial pressures and the pulse rate will in most cases reach a steady state during the work, though this stage is reached later than in the normals. The values at this stage must, like in the

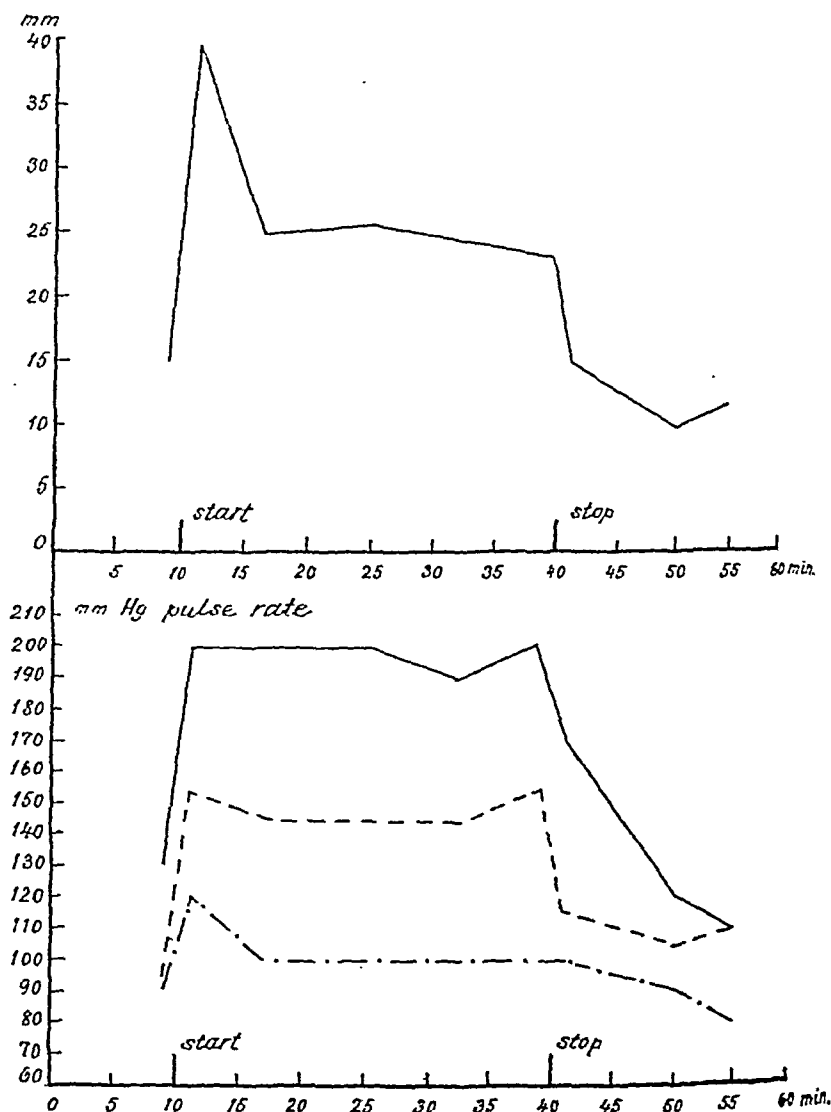


Fig. 3. Variations in the arterial pressures, the pulse rate, and the range of the maximal oscillation in experiment No. 97. Uninterrupted line indicates the 1st pressure, — — — the 2nd pressure, and — · — · — the pulse rate. The abscissa indicates the time in minutes. The ordinate: Lower section = the values of the arterial pressures and the pulse rate. Upper section = the variations in the range of the maximal oscillation expressed in num.

normals, be regarded as the response of the person in question to the given weight.

The average figures for each experiment of the values measured at the steady state show that the results obtained by double expe-

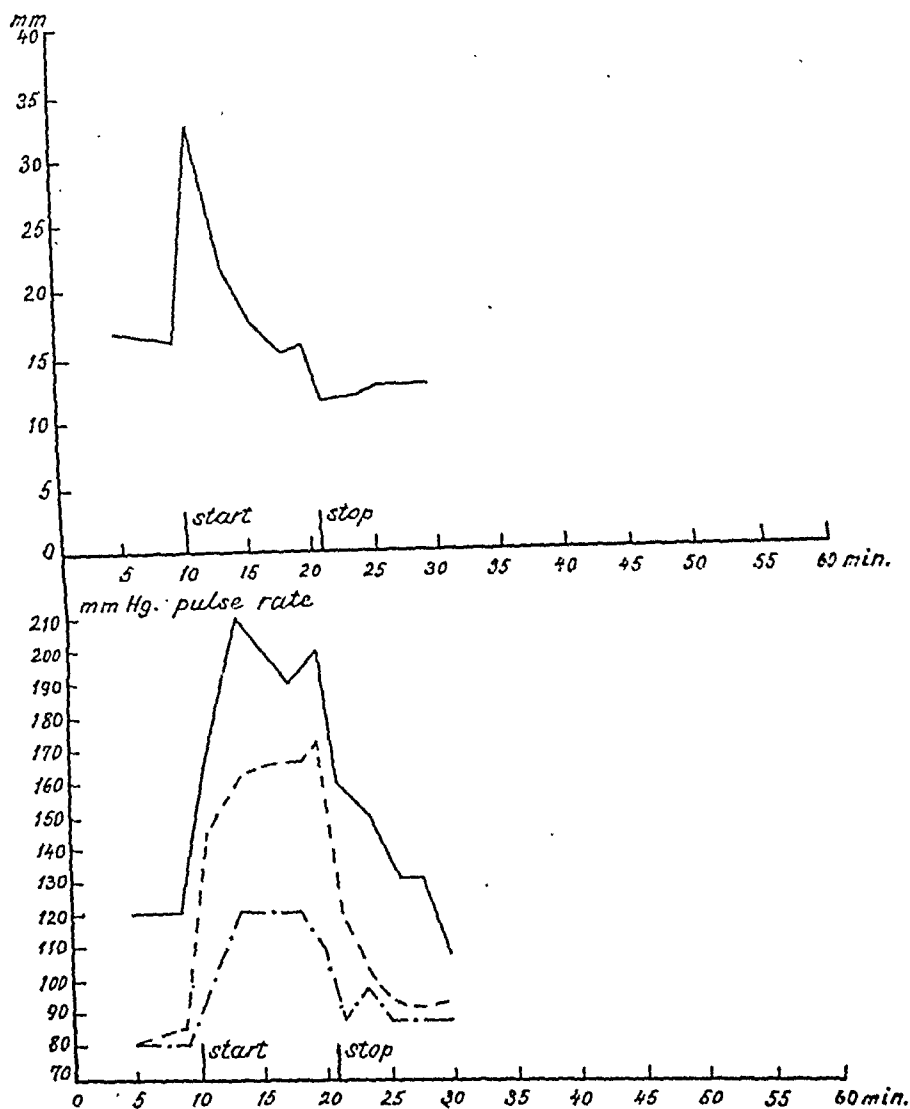


Fig. 4. Variations in the arterial pressures, the pulse rate, and the range of the maximal oscillation in experiment No. 85. Uninterrupted line indicates the 1st pressure, — — — the 2nd pressure, and — · — · — the pulse rate. The abscissa indicates the time in minutes. The ordinate: Lower section = the values of the arterial pressures and the pulse rate. Upper section = the variations in the range of the maximal oscillation expressed in mm.

periments accord well with each other. This accordance makes it possible to calculate for each patient an average resting value and an average working value of each of the 3 functions at each work carried out. These values are found in table 3.



Table 3.

The average values of the arterial pressures and the pulse rate at rest and during the different works.  
8 patients with the effort syndrome.

Patient No.	Work	Number of exper.	1st pressure	2nd pressure	Pulse rate
No. 1. ....	rest	10	92	69	83
	300 kgm.	2	93	63	89
	600 »	3	103	68	129
	900 »	2	129	83	158
	1200 »	3	123	80	170
No. 2. ....	rest	7	81	57	75
	300 kgm.	2	84	53	89
	600 »	3	102	65	115
	900 »	2	127	80	144
No. 3. ....	rest	7	116	79	76
	300 kgm.	1	133	85	96
	600 »	2	170	86	121
	900 »	2	193	112	162
	1200 »	2	195	118	171
No. 4. ....	rest	5	116	77	87
	300 kgm.	1	130	80	116
	600 »	2	139	88	145
	900 »	2	155	100	170
No. 5. ....	rest	6	133	93	98
	600 kgm.	2	176	110	150
	900 »	2	200	122	162
	1200 »	2	198	130	160
No. 6. ....	rest	6	102	72	76
	300 kgm.	2	102	79	102
	600 »	2	129	94	141
	900 »	2	120	89	152
No. 7. ....	rest	6	111	73	86
	300 kgm.	2	118	77	99
	600 »	2	150	85	137
	900 »	2	160	100	183
No. 8. ....	rest	6	106	70	88
	300 kgm.	2	124	77	?
	600 »	2	139	80	142
	900 »	2	158	90	182

Table 4.

The average resting and working values for 6 patients with the effort syndrome.

Works	1st pressure	2nd pressure	Pulse rate
rest	114	77	85
300 kgm.	121	80	103
600 »	151	91	139
900 »	173	102	169
1200 »	197	124	167

A further review of these values shows that patients Nos. 1 and 2 have considerably lower pressures than the normals both at rest and during work. Presumably both of them suffer from a constitutional arteriel hypotension. As for the rest the values measured lie within the range of those found on the examinations of the normal individuals. The variations within the group of patients are seen to be somewhat greater than within that of the normals, but all in all these examinations show that there is no difference between patients and normals with regard to the response of blood pressure and pulse rate to muscular work. The patients are not able to carry out as great amounts of work as the normals, but there are found no signs of a failure of their circulation, not even at the greatest amounts of work that they are capable of performing

By calculating for the group of patients collectively (excepting the 2 with hypotension) the average figures for resting values and for the different working values we get the figures of table 4.

Table 5.

Comparison of the values of the arterial pressure and the pulse rate in normals and in patients with the effort syndrome.

Works	1st pressure		2nd pressure		Pulse rate	
	norm.	pat.	norm.	pat.	norm.	pat.
rest	111	114	77	77	89	85
300 kgm	130	121	87	80	105	103
600 »	142	151	87	91	135	139
900 »	156	173	100	102	159	169
1200 »	168	197	106	124	172	166

A comparison of these figures with those for the normal persons (see table 5) shows that there is no essential difference between the 2 groups. The 1st pressure rises somewhat more in the patients than in the normals, whereas the 2nd pressure, and, what is more astonishing, the pulse rate show the same rise in the 2 groups.

Thus the examinations mentioned here show that patients suffering from the effort syndrome are able to carry out rather great amounts of muscular work, and that the variations in the arterial pressures and the pulse rate are in the main the same as in the normal persons. The absolute rises are of the same magnitude as those found in the normals. Thus on the examinations during muscular work there has been found nothing to suggest that the patients in question should be asthenic in the ordinary sense of this word, which is, indeed, in contrast with the hypothesis advanced by White and other American writers.

### Summary.

A review of the literature dealing with the effort syndrome shows that nothing certain is known as to the etiology and pathogenesis of the affection. More recent investigations suggests that hyperventilation should provoke the symptoms. The occurrence and symptomatology of the affection are mentioned. Further a review is given of the experimental examinations made of patients suffering from the effort syndrome. It appears from these examinations that in some cases there is found a reduced carbon dioxide partial pressure in the alveolar air, and that the patients mentioned here have a respiration type deviating from that of the normals. Some investigators have succeeded in provoking typical symptoms by letting the patients hyperventilate at rest. All the other investigations have shown perfectly normal conditions.

Moreover a brief account is given of the treatment, from which it appears that graded muscular training has resulted in improvement of some of the patients. Confinement to bed aggravates the affection. An investigation into the prognosis of the affection is mentioned. This investigation has shown that in over half of the cases the affection is decidedly chronic.

The author's investigations comprise 50 experiments on 8 normal young men and 53 experiments on 8 young male patients

suffering from the effort syndrome. Both the normals and the patients carried out works of from 300 to 1200 kgm per minute for up to 30 minutes. All the examined patients were able to carry out 900 kgm per minute for from 14 to 30 minutes, and a few even 1200 kgm per minute for up to 18 minutes in spite of the disagreeable symptoms. Thus the physical capacity for work of the patients in question is reduced but very little.

The variations in the arterial pressures and in the pulse rate during muscular work follow the same course as in the normals. The rises in arterial pressures and pulse rate at the different amounts of work correspond to those observed in the normals. In other words these patients are not asthenic.

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From the Medical Clinic (Director: Professor Sven Ingvar) of the Royal University at Lund (Sweden).

## On the Diagnosis of Myelomatosis.

By

ERIK ASK-UPMARK, M. D.

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Almost one century has passed since that day, Oct. 30th in 1845, when Mr. M., a highly respectable tradesman, aged 45, placed himself under the care of William Mac Intyre, thereby furnishing research with the first case of myelomatosis to be analysed clinically by Mac Intyre, chemically by Bence-Jones and eventually post mortem by Shaw and (microscopically) by Dalrymple. The interest devoted to the disorder since is out of proportion to its rare occurrence, to its fatal prognosis and to its inaccessibility to therapy. It is nevertheless easily to be understood if we consider on the one hand the interesting pathophysiological problems connected with its biochemistry, on the other hand the clinical importance of distinguishing myelomatosis from other generalized affections of the bone system, less resistant to treatment, such as osteomalacia, hyperparathyroidism and carcinoma.

The diagnosis of myelomatosis is to be established with certainty only by means of one or both of two signs: the demonstration of the histological character of a plasmocytoma by biopsy and the demonstration of the Bence-Jones substance in the urine. With regard to the histology the recognition of the central position of the plasma cells is no doubt to be considered a most important achievement; references are to be had in the important paper of Apitz. With regard to the Bence-Jones substance it has until

recently been maintained that this «animal matter», as it was termed by Mac Intyre, occasionally might be present also in other disorders of the bone marrow. For reasons developed by Apitz this opinion is without doubt to be looked upon as erroneous: Bence-Jones substance is, when present, pathognomonic for myelomatosis. There are, however, myelomas where Bence-Jones substance is absent and there are cases where the biopsy, most easily performed by sternal puncture, for one or another reason may fail to deliver the evidence desired. In such instances the diagnosis may be difficult enough, particularly so perhaps if the so-called diffuse myelomatosis is about. The present paper intends to deal with the diagnostic pitfalls hence encountered.

Two particularly instructive records of myelomatosis may be quoted to illustrate the matter in question. In one of them the difficulties of the histological diagnosis were apparent, in the other the clinical course has been remarkable and the determination of the level of the citric acid will be pointed upon as a feature liable to facilitate the distinction between myelomatosis and hyperparathyroidism.

*Case 1. Med. Clin. 2751/37, 857/38. Man, aged 55. Pains suggestive of involvement of the bone system for 15 months before death. Generalized osteoporosis. Hyperproteinemia. Bence-Jones substance absent. Two biopsies (costectomies) as well as the preliminary histological examination of the bone system post mortem failed to confirm the diagnosis. Reexamination of the slides from the autopsy: myelomatosis. Admitted Oct. 28th, 1937. Died April 18th, 1938.*

*History:* Family history and past history without particular interest. Doing work in a soap factory. Dietary habits regular and satisfactory (enough milk, dark bread, butter and meat).

Present history started Jan. 1937, i. e. some 10 months before admission, with pains which have dominated the course ever since and have been accompanied by a reduction of weight, appetite and general condition. The pains, starting in the left leg, the thighs and the pelvic region, were dull, rather continuous but rendered worse by movements. In Febr. he had to stop working and go to bed: the pains were to some degree improved by resting but made worse by physical therapy such as baths, massage etc. In May he was transferred to a rural hospital and registered as carcinosis ossium. No X-ray treatment was given but when leaving the hospital about midsummertime he was rather much improved as well with regard to the pains as to the general condition, having regained 8 kg of the loss of weight of about 14 kg before admission. In Aug. he was able to walk, had no pains and a good appetite. About 3 weeks ago,

however, a dull pain reappeared, localized to the lateral region of the chest. About one week ago an accidental false step with the left foot brought about a feeling as if the spine had been broken below the scapular region. During this last week before admission the pains have been severe, excruciating, appearing in frequent attacks, localized to the back, the chest and the lumbar spine, as was also the case during the subsequent course. The pains were rendered worse by movements which were accordingly restricted: it was impossible for him to be up and about and difficult for him to assume a sitting position in the bed. The general condition was becoming worse as time went on, the appetite was impaired, thrombosis of the left leg did appear and he died eventually April 18th.

*Bedside observations:* On admission the general condition was fair, the nutrition and the colour rather good. Blood pressure 140/85, temperature subfebrile, pulse rate about 75, sedimentation rate of the blood 97/124 (in one/two hours). Physical examination of heart, lungs and abdomen essentially normal, only was the scrotum atrophied, both testes being almond-sized and situated in the external part of the inguinal canal. With regard to the bone system the patient was unable to assume a sitting position in the bed. The spine was not tender on percussion but a distinct tenderness was to be registered of the 5th and 6th left ribs in the axillary line.

During the course in the clinic the general condition went down hill. A certain degree of anemia was to be noted, appetite was impaired, weight reduced. The temperature was during the first months subfebrile, during the last months considerably increased (about 39 C°) and presenting a certain undulation. The localization of the pains was at first the costal regions, afterwards elsewhere, particularly the pelvic region. During the last month X-ray treatment was given, otherwise the therapy was confined to symptomatic remedies (anesthetics etc.). He became more and more prostrated, dyspnoea did appear and a pulmonary oedema eventually finished the suffering.

*Radiography:* Various X-ray examinations were repeatedly performed under the experienced supervision of Dr. H. Hellmer, in charge of the roentgenological department. Briefly summarized, normal conditions were to be registered with regard to the lungs, the trachea, the gastroduodenal system, the kidneys and the urinary tract (also by means of urography). The bone system of the trunk, the skull and the proximal part of the extremities did present a considerable generalized osteoporosis and rarefaction. With regard to the extremities this alteration did involve the upper part of the femur, the humerus and the proximal region of the bones of the forearm, generally decreasing towards the periphery. With regard to the spine a compression was noted of the 7th thoracic vertebra, later on also of the 9th thoracic vertebra. The ribs were also engaged, occasionally presenting a distension of the contour, to be felt when examined by palpation. The general impression of the roentgenologists was a destructive disorder of the skeleton «compatible with that of a myeloma or of osteitis fibrosa cystica generalisata».





Fig. 1. Case 1. Skull. General demineralisation and a certain finemottled appearance.

*Biopsy* was performed Dec. 10th and Jan. 21st by means of resection of ribs, obviously engaged by the process as determined by X-ray examination resp. by palpation. The preparations were thoroughly examined in the pathological department by most experienced pathologists but no evidence was to be obtained of osteitis fibrosa, neither of any myeloma.

Sternal puncture was performed March 22nd, the analysis being performed in the department of pathology by professor E. Sjövall, who gave the following testimony: »In the sternal puncture preparations there are to be noted in the usual parenchyma, which has not turned fibrous, a number of rather large-sized, well-limited agglutinations of cells of myeloid type. These cells are big and well equipped with plasma, their nucleus being round. The type of these cells and particularly their tissue-like connection may support the apprehension that they represent fragments of a myeloma.»

*Laboratory records.* With regard to the urine the diuresis was 500—1800 ml. No protein was to be discovered on repeated examinations; Bence-Jones test was always negative. The amount of calcium excreted during 24 hours varied between 0.24 and 0.46 gram.

With regard to the blood the positive observations run as follows: Sedimentation rate considerably increased (93/112—141/154).

Red count/hemoglobin on admission 4.3 mill./80, finally 3.3 mill./60. Red cells size normal (about  $7.6 \mu$ ), reticulocytes 1—8‰.

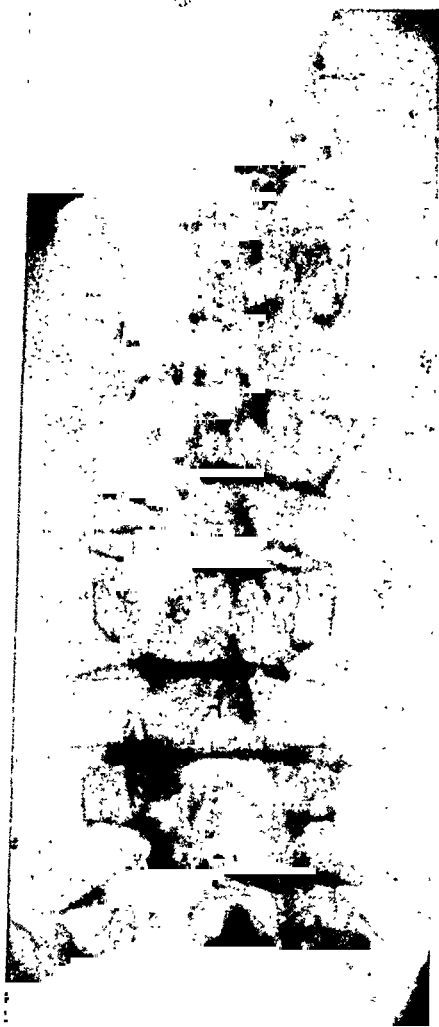


Fig. 2. Case 1. Lumbar Spine. General osteoporosis and a certain compression of the vertebrae.



Fig. 3. Case 1. Left humerus. General decalcification.

White count fairly normal (4900—8100).

Differential count fairly normal. Thrombocytes about 250,000.

Arneth count at first normal (Nov. 12th, I, II, III, IV, V=10, 25, 33, 25, 7), eventually shift to the left (March 27th=15, 44, 34, 7, 0).

Calcium level: Nov. 1937=13.4—11.5—10.8. March—April 1938=15.2—15.1—14.4 mg %.

Phosphate level (determined once only, Nov. 10th)=4.4 mg %.

Non protein N Nov. 2nd=50, Nov. 13th=30, Nov. 22nd=38 mg %.

Serum protein: Nov.=11.2—10.6—10.6, March=11.2—11.6 %.

Oncotic pressure: Nov.=196, 283, 255, March=327.

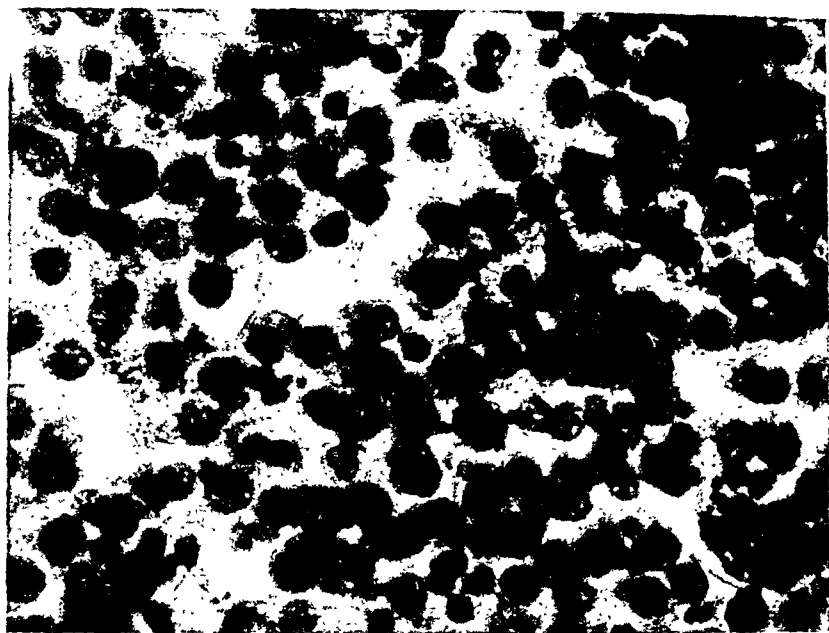


Fig. 4. Case 1. Microscopical appearance of the bone marrow, when reexamined in 1944 by Professor Ahlström.

Takata reaction: extremely pronounced (determined on 4 occasions).

*Necropsy.* Apr. 19th (Department of Pathology): Clinical diagnosis: myeloma. Pathological diagnosis: Osteoporosis praesenilis + Chryptorchismus bilateralis + Thrombosis ven. fem. sin. inveter. + Bronchopneumonia lob. inf. pulm. sin. — The macroscopical observations of heart, abdominal cavity, gastrointestinal canal, liver, biliary ducts, spleen, pancreas, kidneys and urinary tract entirely normal except for a slight enlargement of liver and spleen and some concrements of the gall bladder. Lungs: emphysema, bronchitis, bronchopneumonia; nowhere any bronchial cancer. Testes hazelnutsized. Epididymis, prostata, oral cavity, thyroid, parathyroid regions, suprarenals, pituitary gland, pineal organ and brain macroscopically normal. — The bone system in toto presents a remarkable brittleness and rarefaction of all spongy bone. Thus, the calvaria offers only little resistance to the saw but no localized decalcifications are to be observed. The bodies of the vertebrae are very brittle, the 7th thoracic vertebra being entirely compressed and the 12th thoracic vertebra presenting a certain compression as well. The same fragility and rarefaction of the spongy bone is to be registered in the sternum and the alae oss. ilei, which are easily cut with the knife, and the ribs which are to be broken between the fingers.

Microscopical examination of kidneys, liver, spleen, thyroid, prostate, pituitary gland and pineal organ revealed entirely normal conditions. In

the testes the spermatogenous parenchyma was entirely atrophied whereas clusters of interstitial cells were to be registered. The bone marrow was examined in the femur, in the vertebrae and in the sternal bone: on the preliminary examination hematogenous parenchyma of normal appearance was found but neither any myelomatous tissue, nor any alterations characteristic of osteitis fibrosa generalisata. On the experienced reexamination of the slides, however, kindly undertaken by Professor C. G. Ahlström, plasmacellular infiltrations were abundantly encountered in the marrow of femur, vertebrae and sternum.

*Case 2.* Med. Clin. 1995/41 and forthwith. *Man, aged 55. Accidental discovery of Bence-Jones protein. Subjective symptoms hitherto scanty (observed 43 months so far). Hyperproteinemia. Biopsy repeatedly: characteristic myelomatous tissue.*

*History:* Family and past history of no interest. Working as attendant in a psychiatric hospital. Dietary habits regular and hygienic. Present history: The sedimentation rate of the blood was found to be considerably increased when examined on account of an outbreak of tuberculosis in one of the wards where he was occupied. He had no subjective symptoms with exception of some slight pain and stiffness of the left hip joint during the last few weeks. He was admitted to the clinic Sept. 1st 1941 and has since been observed periodically: 1941 in Sept., Oct. and Dec., 1942 in Jan., May., Sept. and Dec., 1943 in March, 1944 in March and Nov.

*Bed side observations:* On his first admission the general condition was fairly good, the blood pressure 140/100, temperature subfebrile, pulse about 90; weight 77 kg. He had a malum coxae senile, most so at the left side, which may or may not have been responsible for his pains. Physical examination of heart, lungs, abdomen and central nervous system revealed essentially normal conditions. No tenderness of the bones. Able to be up and about without difficulties. A moderate anemia was present (vide infra):

The subsequent course rather much parallels the behaviour of the weight as seen in the table p. 226. It reached its minimum with 63.3 kg. May 1942 and has by now (Nov. 1944) returned to the base line of about 78 kg. The pains have never been outstanding but when most pronounced (May 1942) they were felt in the sacral region, the thorax, the shoulder joints and the knees. For the last one year and a half no real pains have been present only a certain feeling of stiffness when rising from sitting position. On the whole the pains have, when present, rather much been confined to the articular regions (knees, shoulders, fingers, so that he in Sept. 1942 was unable to close the fist). Besides of the (slight) pains the patient has been hampered by tiredness. This was most pronounced in the winter (January—May) of 1942, when the anemia reached its bottom level. The temperature was at first subfebrile (37—38 C°) without any undulations; since Dec. 1942 the temperature has regained normal level. The pulse rate averaged and often exceeded 90; since Dec. 1942 it has, when registered, averaged 80. The working ability was to some



Fig. 5. Case 2. Right hip joint region Sept. 1941. Essentially normal appearance.

degree restored already in Sept. 1942; since Jan. 1943 he has been on duty as usual in the hospital.

*Radiography:* Except of evidences of a *malum coxae* and an old, inveterated fracture of the first lumbar vertebra the roentgenological observations have been scanty, in spite of repeated experienced performances. Sept. 1941 the skull, the spine, the pelvis, the femur and the humerus were reported as essentially normal. Jan. 1942 finemottled decalcification in upper ends of femurs and in the pelvis. May and Sept. 1942 progression of these alterations. Dec. 1942 a similar general decalcification of the spine, causing compression fractures of several lumbar vertebrae; the same affection was to be recognized in both humeri and in the ribs. On later examinations an obvious regress of the changes of the pelvis and femurs was to be registered, status quo condition in other parts of the skeleton except of the skull, where March 1944 one solitary circular rarefaction was to be observed, which differed from the other changes of the bone system as well with regard to the time of its appearance as with regard to its morphology. Nov. 1944 this rarefaction remained unchanged.

*Biopsy* was performed by means of sternal puncture Sept. 1941, Dec. 1942, March 1943, March 1944 and Nov. 1944. Besides of normal cells of the bone marrow there were to be observed cells characteristic of a plasmocytoma (size, tinctorial character, appearance and position of nucleus, inclusions in the protoplasma). Whilst these cells still in Dec.



Fig. 6. Case 2. The same region in May 1942. Destructions easily to be recognized in the Ileum.



Fig. 7. Case 2. The same region in Nov. 1944. Former destructions are to a considerable degree to be considered as restored.

	Weight, kg	Bence-Jones	Sed. rate	Hemoglob.	Red count	White count	Protein, total	Albumin %	Globulin °	Oncotic pr.	Calcium mg %	Phosphate mg %	Phosphatase	Citric acid	Varia
1941 Sept.	77	+	128	73	3.96	5500	9.2 9.5	3 3.1	6.2 6.4	388	11	3.7	4E		
Oct.	74	+	142	77	3.77	6000	—	—	—	395	12.7	4.2	5E	10.5 10.9 13.1	Fe/S 63 <sup>1</sup>
Dec.	71	+	156	65	3.0	3400	9	3.8	5.2	—	12.9	—	5E	10.7	Fibrinogen 0.37 % Fe/S 57. Cu/ S171.
1942 Jan.	66.5	+	162	42	2.62	5100	10.2	2.7	7.5	—	—	—	12E	11.3	Hematocrit 20. Protromb 58 % Chlorides Fe/S 44.
May	63.5	+	155	69	3.9	4000	9.3	1.5	7.8	345	—	—	6E	15	Hematocrit 28. Fe/S 79. Protromb 88.
Sept.	65	—	149	60	3.3	5410	9	2.8	6.2	380	—	—	—	16.4	
Dec.	65.8	+	129	85	4.0	6500	9	3.2	5.8	415	12.8	—	11E	20.4	Fe/S 76. Uric acid 4.4. Cholesterol 160
1943 March	67.1	—	111	96	4.2	4000	6.9	3.2	3.7	—	10.5	3	8E	21.5 18.2	Fe 103 Cu/S 93 Heller + RN 36 Takata -
1944 March	76	—	60	94	4.8	5200	7.7	4.0	3.2	—	9.8	2.5	4E	27	
Nov.	78.6	—	122	79	4.0	4600	>8.2	—	—	—	11.0	—	4E	21	Heller + K 20 mg Takata +

<sup>1</sup> Fe and Cu are indicated as  $\gamma/100 \text{ cm}^3$  plasma.

1942 were arranged in aggregates, they were on later examinations scanty, solitary and nowhere dominating the cellular picture. In Nov. 1944 all these cells had disappeared.

*Laboratory records* may conveniently be summarized in the following table, where also the weight of the patient is to be seen. The differential count, the Arneht count, the thrombocytes, the size of the red cells and the reticulocytes are not recorded, these items averaging normal levels.

The therapy has been confined to iron, on one occasion (May 1942) also to a blood transfusion. No X-ray treatment has been given. With regard to the level of the citric acid it should be emphasized that analgetics such as salicylic acid etc. never were used.<sup>1</sup>

### Comment and discussion.

The cases just quoted may illustrate the following topics:

1. The difficulties sometimes encountered in the histological diagnosis.
2. The occurrence of a diffuse myelomatosis, i. e. without nodular tumour formation.
3. The hitherto undescribed diagnostic importance of the citric acid level.
4. The possibility of a temporary clinical remission in the course of a myeloma.

ad (1). Whilst the diagnosis of case (II) was obvious (Bence-Jones, positive biopsy) the diagnosis of case (I) was considerably entangled. The general clinical impression favoured the assumption of a myeloma: the age of the patient, the rapid course, the fatal outcome and the biochemistry of the blood were items perfectly compatible with this diagnosis. The radiography failed to demonstrate any punched-out areas but this does of course not rule out the diagnosis since a diffuse myelomatosis may be about (vide infra). The costal biopsies, however, seemed to exclude the diagnosis myeloma and neither was any evidence to be obtained for the possibility of a hyperparathyroidism, nor for any metastatic tumours of the bone system, such as carcinosis. As for osteomalacia the general appearance of the skeleton as well as the seasonal amelioration of the symptoms (vide infra) might have represented suggestive evidence, apparently confirmed by the

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<sup>1</sup> When reading the proof sheets in March 1945 the patient has been readmitted with a sedimentation rate of about 140, a protein level of about 11 % and pains when moving or trying to get up from the bed.



costal biopsies, had it not been for the blood chemistry and the impossibility to explain why an osteomalacia should be brought about in this very case. The original diagnosis myeloma seemed however to be substantiated by the sternal biopsy. All the more startling was the result of the necropsy, which failed to reveal any conclusive evidence in this direction and apparently seemed to suggest a praesenile osteoporosis as the disorder of the bone system here in question. Since, however, the clinical course seemed to be much too rapid and too malignant to suit this diagnosis, which moreover would fail to explain the hyperproteinemia, the microscopical material of the present case (still filed in the Department of Pathology) was reexamined under the experienced supervision of Prof. Ahlström, to whom I am indebted for his kind interpretation of the slides. This examination resulted in the observation, in the otherwise fairly normal bone marrow, of clusters of cells of a strikingly uniform appearance. Although the nucleus of these cells in most instances was situated rather much in the centre of the well-developed protoplasm, in which no Russell bodies were to be registered, it was nevertheless felt that the picture was rather characteristic of a myeloma. The impression gained by the earlier examination of the sternal puncture preparation was hence confirmed and the pathology of the case made to converge with the clinical and biochemical features towards the diagnosis of myeloma. It should be observed that the histological recognition of the myelomatous character was to be established not only with the slides from the necropsy but also with the slides from the costal biopsies, where, however, the cells were more scattered. If judged by a less experienced pathologist this case might have been termed »premyeloma»; that the conception of this condition is based on slender evidence only seems to be beautifully demonstrated by the present observation.

ad (2). When it deals with the lymphatic system it is possible to arrange the various neoplastic disorders in three different stages: solitary lymphosarcoma, lymphosarcomatosis and lymphadenosis, i. e. lymphatic leukemia. With regard to the plasma cells the corresponding disorders are the solitary myeloma, the myelomatosis and the plasma cell leukemia. The solitary myeloma or plasmocytoma is a rare condition, even doubted by several authors but

maintained as an important although unusual type by others, since it is considered as to a certain degree available for surgery (Apitz). The plasmacellular leukemia is rare as well; it should of course be distinguished from the plasmocytosis of rubeola, which is a reaction phenomenon comparable to the leukocytosis in many other infections. The myelomatosis, finally, may appear in two different patterns: the so-called multiple myeloma, which is the usual form, and the diffuse myelomatosis, which is unusual and important as a diagnostic pitfall. With regard to the diffuse myelomatosis one has to realize that certain instances, which at the necropsy are revealed as multiple myelomas with the nodular, circumscribed, bone-destructing aggregations of well known appearance, may during life appear as diffuse myelomatosis, owing to certain limitations of the radiographic diagnosis, as set forth by Spiller (1930) and others; this goes particularly for the affection of the spinal column, where the radiogram may be suggestive of osteoporosis only whilst the necropsy may reveal a nodular myelomatosis. Diffuse myelomatosis is, in other words, more common clinically than anatomically.<sup>1</sup> From the point of view of biological analysis only such instances are to be considered as diffuse myelomatosis where the diagnosis has been confirmed by a complete necropsy, including also the skull.<sup>2</sup> As a matter of fact the number of such observations is rather limited, thus in itself justifying the publication of case (I) of this paper, whereas case (II), although clinically rather likely to represent a diffuse myelomatosis, may or may not belong to the by far more common nodular «multiple» type. An attempt has been made to review the autoptically verified cases of diffuse myelomatosis in the following table.

It is perfectly obvious on the one hand that certain instances included in the table may be discussed as to their character of diffuse myelomatosis. Thus, in several cases no information was given about the condition of the calvaria and since this represents a seat of predilection for the myelomatous nodes the diffuse

<sup>1</sup> Thus, otherwise instructive cases like that of Blatherwick (1916) and that of Weissenbach and Lièvre, although watertight myelomatosis, are not included in the review given below since no autopsy was obtained.

<sup>2</sup> Such a case as, for example, Mieremet's (1915) is described as a diffuse myelomatosis but it is mentioned that the calvaria did present «hin und wieder rötlich erscheinende Stellen, die graurötliche, weiche Massen bis zu Kirschengröße enthalten». Such a case is accordingly not included in the table below. The same goes for Wallgren's case VI.

*Casis of diffuse myelomatosis, verified by autopsy.<sup>1</sup>*

	Year	Author	Sex	Age	Duration	B. J.	Histology	Remarks
1)	1850	Mac Intyre	M	45	14 months	+	(+)	First case of myeloma ever described. S?
2)	1883	Runeberg	F	58	1 month		(+)	«Medulläre Pseudo-leukämie». Heller +
3)	1893	Stokvis Ribbink Zeehuisen	M	39	?	+		Paramyloidosis. Chalky deposits in Kidney. S?
4)	1894	Rachke	F	65	6 months	+		«Senile osteomalacie». S?
5)	1895	Stintzing	M	65	?	+		Quoted by Bradshaw S?
6)	1898	Parkes Weber	M	61	3 months			«General lymphadenomatosis of bones, one form of multiple myeloma». Heller neg. S. nodular?
7)	1899	Bradshaw a. Warrington	M	70	20 months	+	(+)	S?
8)	1899	Askasazy	?	?	?	+	(+)	«Lymphatische Leukämie». «Nirgends circumscripte Tumorbildung».
9)	1901	Kalischer	F	67	1½ year	+	(+)	S?
10)	1902	Jochmann u. Schuman	F	37	1½ year	+	(+)	S?
11)	1903	Abrikosoff	M	54	6 months	?	+	S?
12)	1909	Tchistowitch u. Kolessnikoff	F	36	2 years	+		Calcinary deposits in lungs, kidneys, wall of stomach, papillary muscles of the heart. S?

<sup>1</sup> Symbols: B. J.=Bence-Jones. S?=no information about the skull. Histology: +=plasmocytoma, (+)=earlier description which may be deduced to represent plasmocytoma.

(Concl.)

	Year	Author	Sex	Age	Duration	B. J.	Histology	Remarks
13)	1911	Berblinger, case I	M	55	?	?	+	Cirrhosis hepatis
14)	1912	Versé, case III		16	6 months	?	+	
15)	1914	Bomhard, v.	F	51	1 year		+	One nodule in one rib
16)	1920	Wallgren, case III	F	50	1 year	?	+	Heller + S?
17)		case IV	M	67	3 weeks?	+	+	Mesenterial lymph. node involved
18)		case VIII	M	58	5½ years?	—	+	
19)	1928	Enneking	M	46	3½ months	—	+	Heller + S?
20)	1931	Reiche	F	74	3½ months	?	(+)	•Akute calciprive osteopathie. Hyperproteinemia (11.4%, of which 8.5% = globulins)
21)	1932	Cabot, case 18491	F	50	5 months	?	+	Diffuse plasmocytomatosis. S?
22)	1934	Magnus Levy	F	46 <sup>1</sup>	1½ year	?	+	Paramyloidosis. S?
23)	1935	Faust	M	50	?	—	(+)	Heller +. •Geschwulst-ähnliche Knochenmarkshyperplasie. In serum Globulines: Albumines = 6: 1.
24)	1935	Spiller u. Revetas	F	60	?	?	+	Died in uremia. Heller +. S?
25)	1936	Robertson a. Brunsting	M	44	2 years	+	+	Paramyloidosis. S? Solitary myeloma?? <sup>2</sup>
26)	1944	Ask-Upmark case I	M	55	15 months	—	+	Hyperproteinemia. Repeated biopsies negative.

<sup>1</sup> Case Frau Brch., indicated as aged 46 p. 80, as aged 38 p. 93.<sup>2</sup> •A softened marrow in a vertebra was the only sign of lesion to be found in the bones; this marrow contained a large increase in plasma cells suggesting a cryptic origin for the proteinuria. • But for 2 years he had had pains in shoulder- and hipgirdles and a diffuse myelomatosis seemed to be probable.

character of the pathological process may be questioned; moreover in case (6) it may be discussed whether not such calvarian nodes were really present and the case (8) ought perhaps better have been termed plasmacellular leukemia. On the other hand it should readily be admitted that cases deserving their place in this table might have escaped my attention; several cases of diffuse myelomatosis are of course likely to escape publication.<sup>1</sup> With these reservations the question may be raised whether there are any significant clinical differences between the diffuse myelomatosis and nodular («multiple») myelomatosis.

With regard to sex 14 were males, 11 females. Since myelomatosis is about twice as common in men the percentage of female cases may seem a bit high but on the other hand the limited size of the material does not seem able to admit any definite conclusion on this point. The same goes with regard to the age; the average age is usually given as 55 years; 11 were 50 years or less, 14 more than 50 years, the average age of all cases being about 53 years. As to the duration the average history is indicated to about 2 years. That it may be longer than that also in diffuse myelomatosis is indicated by Wallgren's case VIII where the duration was 5 ½ years; if however this case as well as the other extreme case (Wallgren IV, 3 weeks?) are excluded it will be seen that out of 7 male cases only one reached a duration of 2 years and only three a duration exceeding 1 year; out of 10 female cases only one lived for 2 years whereas the duration for 6 instances was 1 year or less. The average duration of all instances (cases 17 and 18 excepted) was not quite one year. It will thus appear, with due reservations owing to the size of the material, as if the average duration would be briefer in diffuse myelomatosis than in myelomatosis in general («multiple», i. e. nodular myelomatosis).<sup>2</sup> With

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<sup>1</sup> It might be discussed whether a case like Tschudi-Madsen's should have been included: with all probability it did represent a case of what is now known as polymorph plasmocytoma, but the peculiar ossification within the neoplastic tissue makes it reasonable to place this case in a group of itself. It concerned a man, aged 36, duration 6 months.

<sup>2</sup> The more malignant course of the diffuse myelomatosis may possibly be connected with a generally reduced resistance of the body. Furth found in myelosis in mice that the transmission of the disease to another animal did result in multiple myelosarcomatosis of the bone system, if the receiving animals were previously not X-ray treated. If such was the case, however, and the resistance accordingly lowered, a typical myelosis ensued. In the present case (1) one may ask whether perhaps the cryptorchismus might be

regard to the occurrence of Bence-Jones proteinuria it was looked for in 16 instances, in 12 of which it was encountered, it is thus at least as often present in diffuse myelomatosis as in myelomatosis in general, where its occurrence is indicated as about 2 cases out of 3.

The macroscopical appearance has been described repeatedly and may only be briefly summarized here by quoting the unsurpassed description of Mac Intyre: »— all the ribs, throughout their whole length, were soft and brittle, so that they could be easily cut by the knife, and readily broken, at any point, by the exertion of a very moderate force. They had evidently lost much in size and weight, as well as in consistence and tenacity; their outer encasement, or laminated portion, was very thin, loose and fragile, yielding and crackling when pressed between the fingers and thumb; their interior was charged with a soft gelatiniform substance of a bloodred colour and unctuous feel.» The localization of the affection is the bone system, occupied by red marrow. The neoplastic tissue is often rightly described as resembling splenic pulp, which may be squeezed out of the ribs by slight pressure, as paste from a tube. The bony substance is reduced and fragile and the cancellous tissue may almost have disappeared. Spontaneous fractures are accordingly common<sup>1</sup> as well as deformations (thoracic vertebrae wedge-form, lumbar vertebra »fish vertebra» etc.). Hypercalcemia may be encountered and calcinary deposits have been met with in the kidneys, in the wall of the stomach, in the lungs and in the papillar muscles of heart (cfr case 3 and case 12). These features with regard to the calcium metabolism should be remembered, since they may be liable to mistake the disease for hyperparathyroidism, all the more since the diuresis may be increased as well (as, for example, in Mac Intyre's case). Other complications are paramyloidosis (so-called

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of any importance in this regard: on the one hand Agduhr as well as Störtebecker have emphasized the importance of the sex hormones in connection with the resistance to the action of noxious agents, on the other hand an influence of sex hormones on the bone towards hyperossification has been noted in certain animal experiments (Evans et al., *Endocrinology* 1942). It should be observed, however, firstly that the interstitial cells were preserved in the present case, secondly that diffuse myelomatosis may occur also in individuals of comparatively young age and with numerous offsprings, as for example in Mac Intyre's case.

<sup>1</sup> Which may heal by callus. Bone formation within the tumour may in very rare instances occur.

»primary» amyloidosis), which sometimes may occur, and finally the »Speicherungsnephrose» with its resulting »nephrohydrosis» of the kidney in connection with the elimination of Bence-Jones protein.

ad (3). The differential diagnosis of the generalized disorders of the bone system is of paramount importance to therapy. Hyperparathyroidism thus requires surgical intervention and the same may be said of certain other endocrine disorders where an osteoporosis may be about (such as hyperthyroidism and, under circumstances, Cushing's syndrome). Osteomalacia represents a deficiency syndrome, whatever be its ultimate cause (insufficient food supply, disorders of the intestinal tract or of the liver) and should be treated accordingly. Carcinosis ossium is frequently available to radiological therapy, not least so when the primary tumour has been represented of a cancer mammae. Myelomatosis, finally, represents prognostically a most fatal disorder, somewhat similar to the malignant gliomas of the central nervous system, and the only therapy which hitherto can be offered is as symptomatic as in that case of Mac Intyre 100 years ago which was treated by iron, quinine and Dover's powder. As mentioned above the only watertight diagnosis of myelomatosis is to be performed by one or both of two signs: the presence of the Bence-Jones protein in the urine and the histology as demonstrated by a biopsy. In instances such as case (1), where both these pathognomonic features failed to reveal the true character of the disease one has to rely upon the general clinical features, the anatomical characters and the biochemical tests. It is beyond the scope of this paper to deal more closely with the details implied by this differential diagnosis. It may be sufficient to remember that the general clinical features in myelomatosis may be almost identical with those encountered for example in hyperparathyroidism, that the radiography in diffuse myelomatosis may be impossible to distinguish from the general osteoporotic conditions induced sometimes by hyperparathyroidism, not infrequently by carcinosis and always by osteomalacia<sup>1</sup>, and that several biochemical characters, as for example

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<sup>1</sup> The general belief that the nodular myelomatosis with its punched-out rarefactions of the bone substance should present a picture pathognomonic to »multiple myeloma» may be doubted since entirely similar radiograms occasionally may be found in carcinosis, as seen for example in the excellent monography of Snapper on disorders of the bones.

the presence of hypercalcemia, may occur in myelomatosis as well as in carcinosis and hyperparathyroidism. It should be emphasized as was done by us already some 14 years ago, that should any doubt exist about the presence of hyperparathyroidism a surgical exploration of the parathyroid glands has to be carried out.<sup>1</sup> There are, however, certain biochemical features by means of which a reasonable certainty about the diagnosis in otherwise doubtful instances may be arrived at. Thus, the serum phosphate level is often reduced in hyperparathyroidism, never reduced in carcinosis and always normal or even increased in myelomatosis. The plasma protein level may or may not be considerably increased in myelomatosis. The phosphatase is increased in hyperparathyroidism and, occasionally, in carcinosis, never however in myelomatosis. To these features may be added the observation made in case (2) of the present material that the citric acid level, so important in clinical diagnosis elsewhere (liver disorders, etc.), may be considerably reduced in myelomatosis whilst it on the contrary may be quite enhanced in hyperparathyroidism, the last mentioned observation being made by Sjöström. Since it has been demonstrated, by Alwall, that the administration of salicylic acid preparations is liable to reduce the citric acid level in the blood [the same goes with regard to the prothrombin as recently demonstrated by Link et al. (1943) and Rappert et al. (1943)] and since the disorders of the bone system generally are painful, hence inviting to the administration of analgetics, this source of error should be considered when determining the citric acid level in such a case. It has been pointed out by Dickens (1940) and Thunberg (1941) that the bone system has a very high content of citric acid (about 1 % of dried bone substance, from which the fat has been removed). Considering this fact as well as the beautiful demonstration by Thunberg of the citric acid content in the egg-shell of different birds and in the «cancer stones» of the stomach of the craw-fish, which organs act as a calcium deposit (in the case of the «cancer stones» reversible) the behaviour of the citric acid level in disorders of the skeleton obviously assume enhanced biological interest suggesting a close connection between the calcium metabolism and the citric acid metabolism. From clinical point of view the

<sup>1</sup> The possibility of a compensatory hypertrophy in other bone-consuming disorders should be remembered and not mistaken for an adenoma.



reduction of the citric acid level in myelomatosis is of interest diagnostically (*vide supra*), it is necessary, however, to emphasize, firstly, that a normal level of citric acid does by no means rule out myelomatosis [*cfr* the variations of the level in case (2)], secondly, that further observations will be necessary on the subject.<sup>1</sup>

ad (4). A most striking feature in case (2) has been the long period of improvement, from the patients point of view an apparent recovery. That remissions may occur in the ultimately fatal course of myelomatosis is a well known fact, mentioned by Geschichter and Copeland in their monograph on tumours of the bone and exemplified already by the case of Mac Intyre: »Under this treatment he improved rapidly; the pains become daily less severe, and by the middle of the summer he had recovered so much that he was able to travel to Scotland. There, on the sea-coast, the improvement advanced and for some time he was capable of taking active exercise on foot during the greater part of the day, bounding over the hills, to use his own expression, as nimbly as any of his companions. His appetite, which had at no time failed, became extremely keen, and he indulged it without restriction, particularly with the article of fish. This progress towards recovery was, however, suddenly checked by an attack of diarrhoea — — —. In september he returned to London, in a very debilitated state, but free from the excruciating pains which had tortured him during the spring and early part of the summer. He was again put by Dr Watson on a course of tonics and seemed to be gradually improving, when he was seized, a few days before I saw him, with the lumbar and sciatic pains under which we found him suffering so severely.»

Similar periods of temporary improvement have since been described by others, for example by Bradshaw and Warrington and by Wallgren. In our own case (1) a marked remission was to be noted and similar remissions have been noted repeatedly in previous cases of myelomatosis, observed in our clinic. As a rule the remission does occur only once, but when the duration of the history is long, as in Wallgren's case VIII, repeated periods of amelioration have been noted. It may be an accidental coin-

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<sup>1</sup> In three more instances of myelomatosis, recently observed the level of the citric acid was decreased in one, within normal levels in another case and slightly increased in the third case (33).

vidence but we have the impression that the remission is particularly liable to take place in the summer; such was the case in Mac Intyre's case, in Wallgren's case VIII (case 18 in the table 00), in our own case (1) and in some cases previously observed by us; Bradshaw's and Warrington's case likewise at first improved in the summer but eventually turned down hills and died in August. In several instances, where the course is more rapid, no remission is to be observed and occasional improvements at other seasons may be recorded as well. If, however, the observation is to be confirmed that improvements have a predilection for the summer this is of a certain interest since the same seasonal amelioration may be observed in hyperparathyroidism and is the rule in osteomalacia. The occurrence of a temporary remission is hence by no means unknown. That our case (2) nevertheless is quite remarkable in this regard is due to the duration of the remission. As a rule this duration amounts only to some few months, only in Wallgren's case VIII, which had in itself a remarkably long history, seems a longer period of improvement (approaching one year) to have been noticed. In our own case (2) the duration of the remission so far exceeds two years and is still going on<sup>1</sup>. It is moreover remarkable that the improvement in general condition, to be elicited particularly from the weight and the freedom from pains, has been paralleled by such objective features as the plasma protein level, the relation between the globulins and albumins, the sedimentation rate, the red count and the hemoglobin, the roentgenological signs and the histology as recorded by biopsy (sternal puncture). It should be observed that no X-ray treatment has been allowed to interfere with the course. As a matter of fact we have never been able to convince ourselves about the usefulness of this therapy in myelomatosis.<sup>2</sup>

As a matter of fact, the occurrence of such remissions in the course of a malignant tumour seems to be a most remarkable feature, characteristic for no other neoplastic disorder. The symptomatological remissions to be noted during the course of certain

<sup>1</sup> Cfr. p. 227.

<sup>2</sup> If our apprehension about the seasonal predilection of the remissions will be found to be correct it is possible that ultraviolet rays may be of more avail. An attempt to treat this disorder with large doses of gonadlan hormones (cfr. certain instances of carcinosis) seems so far not to have been made. Solitary instances have been treated with radlostrontium.

intracranial or spinal tumours such as meningiomas and cystic angiomas or gliomas are of entirely different character, reasonably being due to vascular conditions in connection with the peculiar intracranial pathophysiology. In myelomatosis, on the other hand, one is under the impression that the body is about to get rid of its terrible enemy, although the efforts unfortunately are in vain, and the tumour is winning in the long run. Could nothing be done to help the body in its fight? So far we know of no remedies but it is not unlikely that the curious remission to be noted in myelomatosis together with the peculiar protein conditions met with in this disorder may represent a key-hole to the enigmatic problems of tumours in general — although still awaiting the key.

### Summary and conclusions.

1. The diagnosis of myelomatosis is to be established with certainty only by one or both of two pathognomonic signs: the occurrence of Bence-Jones protein in the urine and the histological examination of specimens, obtained by biopsy. A somewhat widespread belief about the occurrence of Bence Jones in other conditions of the bone system is erroneous.

2. Attention is called to the occurrence of diffuse myelomatosis. Clinically, this condition is present when no localized, punched-out areas are to be found roentgenologically. Anatomically, nodular aggregations of neoplastic tissue may be found also in instances, judged as diffuse myelomatosis clinically. In rare cases also the anatomical character is altogether that of a diffuse infiltration of the bone system. In order to establish this condition with certainty the necropsy will have to include also the skull. A review is given of instances likely to represent diffuse myelomatosis, the first case being observed by Mac Intyre-Bence-Jones-Dalrymple.

3. A case of diffuse myelomatosis is described (case I) where Bence-Jones was absent and where repeated biopsies and even the preliminary post mortem examination failed to confirm the clinical diagnosis; on re-examination of the slides from the necropsy the matter was however established. The diffuse myelomatosis appears on an average to run a more rapid course than the nodular («multiple») myelomatosis.

4. The diagnostic pitfalls in such instances are discussed. The citric acid level of the blood may be reduced in myelomatosis, as described in case (II), whilst it as a rule is increased in hyperparathyroidism.

5. The enigmatic occurrence of a temporary remission in the course of myelomatosis is demonstrated by a case (II) where the improvement so far has lasted for more than two years, no X-ray therapy being used. Myelomatosis stands out solitary among malignant tumours in this regard.

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From Sandnessjøen Hospital, Sandnessjøen (Norway). Head: Ragnvald Bakke M. D.

## Three cases of arachnodactylia.

By

TRYGVE KAHRs.

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In 1896 Marfan demonstrated at the Société Médicale des Hôpitaux de Paris a complex of symptoms under the name *dolichosténomélie* (*dolichos*): long, *stenos*): thin, slender, *melos*): extremity). The condition was understood to be a skeletal anomaly, especially characterized by long, spare extremities and long hands and feet.

Two sisters with a similar *facies morbi* were described in 1902 by Achard who created the term *arachnodactyli*. He was the first one to establish that the disease was of a hereditary nature and was found in certain families. Later on his cases have been called in question, but nevertheless is the name — especially in English and German literature used as a collective term for the whole syndrome.

That skeletal changes are often combined with ocular symptoms and then especially with dislocation of the crystalline lens was established by Börger in 1914.

Weve is the first one to leave the descriptive designations and to endeavour to create a name based on the pathogenesis of the syndrome. In 1931 in his monography he proposed the term *dys-trophia mesodermalis congenita, typus Marfan*. He regarded the disease as an independent, systemic disease arisen on a congenital basis, and essentially caused by an abnormal development of the mesodermal seminal leaf. Weve is the first one to have shown by

systematic research in the families, where arachnodactyli is found, that besides the typical cases there are a number of «formes frustes». In these individuals only certain of the characteristics are present, but they are in the same high degree carriers of the characteristic hereditary dispositions of the disease.

Till now about 200 cases have been described in literature, and in Scandinavia the disease has been commented on 8 or 10 times. On account of the comparative rareness of the syndrome a short summary is given of the rich symptomatology of this disease.

It is advantageous to divide Marfan's syndrome into 3 groups of symptoms, the presence of which is necessary for a sure diagnosis.

### 1. Skeletal symptoms.

These consist of increased longitudinal growth, and extremities that are remarkably long and slender in proportion to the trunk. The extension is more decided in the distal than in the proximal parts. This causes the long hands and feet (spider hands, *pattes d'araignée*). Where the disease is localized to the extremities only, the height of the body can be normal or even lower on account of secondary kyphosis.

### 2. Badly developed and hypotonic musculature combined with loose ligaments.

In connection with the erect walk appear kyphosis and scoliosis. The joints frequently show hyperflexibility, which is partly conditional on the bad muscular tonus, and is partly due to a constitutional deficient development of the articular capsules. The hyperflexibility may be so considerable, that spontaneous luxations may arise. In spite of the spare appearance of the muscles the power is remarkably good, and the muscles never show any reactions of degeneration.

### 3. Missing subcutaneous fatty tissue.

This appears already at birth, but in other cases may not appear till infancy. In the face the lack of fat is least pronounced, and this is in contrast to the rest of the body. However, an oldish facial expression is mostly found already from infancy. In rarer cases panniculus adiposus is intact. Some of the persons affected have webbed hands and feet. All these patients seem to be suffering from asthenia, and the condition has been understood to be an extreme degree of leptosomy.

Besides the inevitable symptoms a number of secondary symptoms occur with alternating frequency. In about 80 per cent. the cranium is dolichocephalic. The face is long and narrow and is often distinguished by a long nose and prominent chin. The auricula may be deformed with strong development of crus helcis, which seems to divide the auricula in two. The palate is high and arched, and uvula is often bifid. Among the more facultative skeletal symptoms may be mentioned deformation of the chest, scapula alata, spina bifida occulta, pes planus and digitus malleus. The Achilles tendon is projecting spur-like, and the big toes and the thumbs are often disproportionally long. In the fingers are found contractures in the interphalangeal joints of the 4th and 5th fingers (*kamptodactyli*). According to Schienz there is no osseous ankylosis. The growth of tendons and articular capsules does not proceed at the same rapid pace as that of the bones, and thereby a gradual flexion of the joints takes place. Contractures in the big joints are more infrequent.

Ocular symptoms appear in about 40 to 50 per cent. of the cases, and they are dominated by dislocation of the crystalline lens. Weve states that luxation of the lens mostly appears in the grave forms of *arachnodactyli*, and they are only seldom seen in connection with *formes frustes*. The lens may be displaced to every side, but as a rule upwards and towards the nose. The distinguishing feature of the luxation is, that it is two-sided and symmetrical. Where the lens is luxated into the anterior chamber, an acute increase in pressure is caused, which may indicate an operation. Also high-degree myopy and miosis occur. The myopy is explained partly as a refractive myopy, the bulb of the eye being enlarged in proportion to the lens, and partly as a lens myopy on account of the sphericity of the lens after the luxation. The pupils react as a rule badly on *mydriatica*. Secondary after the luxation there may occur atrophy of the iris, degenerations of retina and *atrophia nervi optici*, which lead to complete amaurosis. Cataract in the luxated lenses is not infrequent. The bulb of the eye is deep in orbita, partly owing to lack of orbital fat, and partly owing to an abnormality in the osseous part of orbita, this arching convexly up in the anterior cranial fossa. More seldom are seen *megalocornea*, *strabismus*, *nystagmus* and persisting *membrana pupillaris*. Weve states that the lateral part of the palpebral fissure under the effect of

Marfan's syndrome is lower than the medial one in contrast to the palpebral fissure of the mongoloids.

In about 30 per cent. of the cases congenital defects of the heart are found, either an interventricular defect or persisting ductus arteriosus. Cyanosis owing to stenosis of the pulmonary artery is more infrequent. Further, anomalies of the lung with defective pulmonary borders and poor development of the right middle lobe have been described. The basal metabolism can be lower than normally, and this has been cited in favour of the disease having its origin in the thyroid gland. The blood pressure is as a rule low. The contents of calcium and phosphorus in the serum are always normal.

The nervous system and sexual life are usually normal, and there is no lack of secondary sexual features. Combinations with syringomyelia and Friedreich's disease must probably be a coincidence. Nor has any connection between arachnodactyli and myatonia congenita, Oppenheim been established, no luxations of the lens ever having been found in cases of myatoni. The mind is described by most authors as being normal. A few of the affected individuals are suffering from oligophreni, and in Filskov's case a reactive psychosis developed caused by the skeletal symptoms.

By X rays the compacta of the bones are found thinner, and the medullary cavity is broader than usual, but otherwise the bone structure is normal. The bones are lengthened, and this is especially remarkably in the case of the metacarpal bones and the phalanges. Epiphyses have a normal appearance, and the centres of ossification appear at the right time. In reality fingers and toes seem to be longer than on the Roentgenogram, as the lack of subcutaneous fatty tissue gives further prominence to their length and slenderness. Frontali has shown epiphyses in both ends of the phalanges and has considered this as a cause of the increased growth, without this having later on been verified. Sella turcica is always of normal size.

Very few sections have been undertaken in connection with Marfan's syndrome. These have confirmed the presence of the heart- and lunganomalies, but they have not otherwise thrown any further light on the pathogenesis of the disease.

The anomaly predisposes for pulmonary sufferings, and the most common cause of death is pneumonia. The affected children



are feeble from birth, and they learn late to sit and to walk. The length at birth is frequently remarkably great, while on the other hand the weight is comparatively small. Most of the children die before they are grown. If these individuals reach grown age, however, the prognosis *quo ad vitam* is considerably better, and they may attain as high an age as other people. The viability of *formes frustes* is far greater than in the case of a fully developed syndrome, and it depends on the condition of heart and eyes, whether these individuals become invalids or not.

Therapeutically little is to be done. The most important thing is a rational protection of the children against infections of the respiratory tract, benign colds and bronchitis having a tendency to progress. Luxations of the lens may in many cases be corrected by glasses. Where the lens is luxated forwards into the anterior chamber, extraction may be indicated. Orthopaedic operations to correct contractures and deformities are more seldom.

Patient No. 1. P. H. age 56, fisherman.

On his father's side there have always been long, thin people, but they have all had good eyesight. He is married to his cousin, who is small and stoutish. They have had four sons, and two of them have been suffering from this disease. From birth he has been long and thin and has had poor eyes. In 1933 two-sided luxation of the lens was diagnosed. He has always been of good health, and has done heavy work without having been handicapped by weakness.

Height: 187.5 cm. Weight: 69.1 kilos. Shoe measure 47. The skull is brachycephalic (index 82.1), and he has a long and narrow face (index 103.7). The palate is high and arched. The teeth are missing. The thyroid gland is normal of size and shape. Pulse 78, regular, large. Blood-pressure 175/70.

Cor: No dullness. In the 2nd intercostal space a diastolic, *descrescendo* murmur. Ictus cordis in 5th intercostal space in the mid clavicular line. The peripheral symptoms of insufficiency of the aortic valve are present.

He has the typical deformity of the thorax (cfr. fig. 1) with small respiratory movements. There is a right dorsal and left lumbar curved scoliosis. The right scapula and the posterior part of the thoracic wall are more prominent than that of the other side. Pulmones and abdomen: Normal conditions.

Urine: Albumen- Pus- Blood- Sugar-, Wassermann reaction-.

The musculature is lax and poorly developed, but the power is good. In the middle joint of the left little finger there is a 45° permanent flexion. The hands are spare and distinctly arachnodactylic (cfr. fig. 2). There is a high degree of *pes planus bilateralis* with *digitus malleus* of 2nd and 3rd toes. The arm length is 91 cm and the length of the leg 110 cm.



Fig. No. 1. P.H. Note the high-degree kyphosis and the deformed thorax.

Eyes: Conjunctiva and cornea are normal with the exception of considerable arcus senilis. The anterior chambers are deep, and there is a decided iridodonesis on both eyes. The lens is spherical and is on the left side luxated straight outwards, and on the right side outwards and upwards. Both lenses are full of whitish cataract substance. He is able to distinguish fingers in a distance of about 1 metre *oculi uterque*, and this cannot be increased by correction. The pupils react well upon light and upon mydriatica. The tension is normal.

Roentgen shows the typical arachnoidactylic changes of hands and feet. X ray of the heart shows a configuration usually found in diseases of the aortic valve without any signs of enlargement of the heart or dilatation of aorta.

Patient No. 2. R. H. Eldest son of No. 1.

Since birth tall and thin. Photography at nine years of age shows the changes typical for the anomaly, as far as the hands are concerned. The luxation of the lens was diagnosticated in 1933, and later he wore glasses. On examination of his glasses these are found to be the kind worn by persons without any lenses (+ 11 D). Retrospectively it must be concluded, that this boy suffered from Marfan's syndrome. He died of pneumonia in 1939 at the age of 19.

Patient No. 3. S. H. Youngest son of No. 1. 9 years old.

He has been thin and weakly since birth. No previous illness. Admitted to the hospital at Sandnessjoen in December 1942 and operated on for

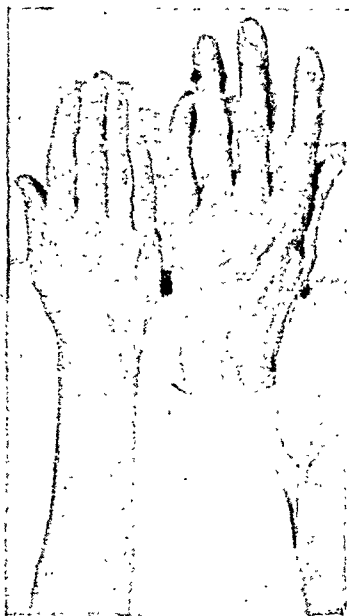


Fig. No. 2. P. H. To the left the patient's hand besides the author's.

acute appendicitis with peritonitis. The patient is in a miserable condition, and panniculus adiposus is lacking entirely.

Height: 149.5 cm. Weight: 27.2 kilos. The height corresponds to a physical age of 13.4 years and the corresponding weight is 40 kilos. Normally a boy of nine is 130—135 cm. As shown in photography No 3 this great height is due to the considerably increased growth of the lower limbs in proportion to the trunk.

He has the same cranial and facial form as the father (index respectively 82.8 and 97.6). The position of the teeth is irregular, and the palate is high and arched. The chest shows the same deformity (cfr. fig. 3), and there is a dorsal kyphosis and a right curved scoliosis. He has webbed hands, and there is a great hyperflexibility of hands- and fingerjoints. Both big toes are abnormally long, and the other toes show digitus malleus. Further he has a heavy bilateral pes plano-valgus. The arm length is 67.5 cm and the length of the leg 82 cm.

The eyes show nothing pathological. Visus is uncorrected 5/5 oculi uterque.

Pirquet — Blood pressure 110/70. Haemoglobine 110-per cent.

Urine: Albumen — Pus — Blood — Sugar —

Roentgen shows the increased longitudinal growth of the peripheral parts of the extremities. There are no double epiphyses in the phalanges. No spina bifida occulta or enlargement of sella turcica.

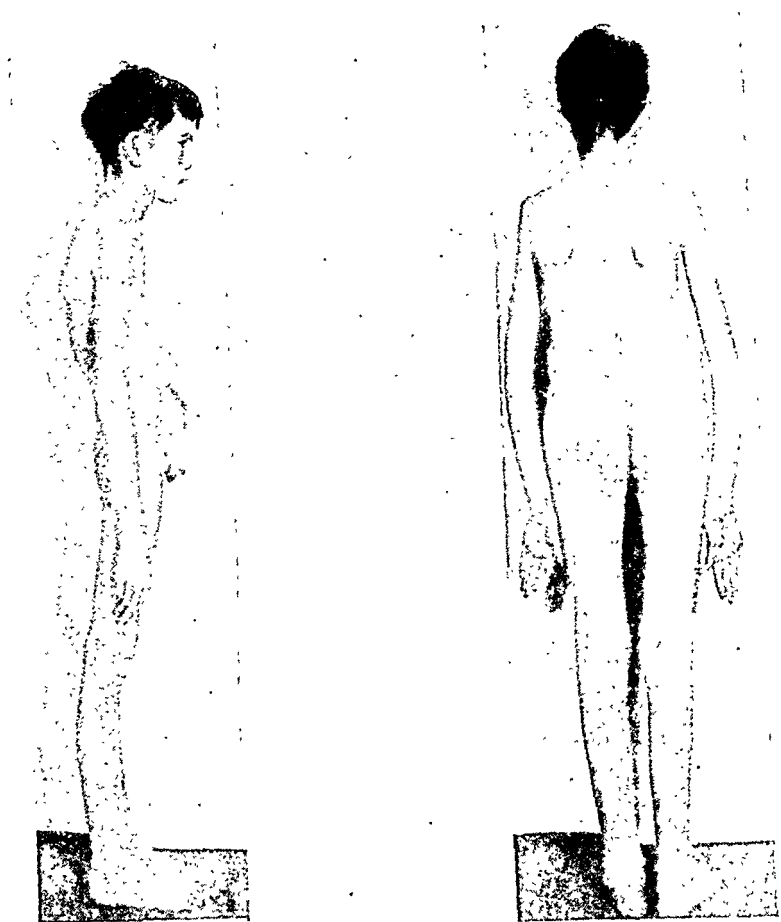


Fig. No. 3 & 4. S. H. Note the long extremities and the lax carriage.

*Epicrisis:* Three cases — a father and two sons — of Marfan's syndrome have been described. The father and the deceased, elder son showed the skeletal symptoms combined with luxation of the lens, while the case of the younger son presented skeletal changes only.

There exist several theories regarding the cause of Marfan's syndrome, but none of them may be said to be fully recognized. The fault with all of them is, that the theories are mainly based on hypotheses and suppositions without any positive experimental basis. Exogenous elements as lues, rickets, marriage between

relatives etc. have been discussed, but they are now assumed to be without importance. Nor is the earlier described preponderance of the syndrome in females in accordance with facts, the disease being equally divided between the two sexes. In about 30 per cent. dominant heredity in accordance with Mendel's law of heredity is found. By the recognition of the larvated forms, where only a few symptoms are present, the certainty of the hereditary nature of the disease has increased further.

Weve supposes that the disease is an independent congenital, systemic disease caused by an abnormal development of the mesodermal seminal leaf. The only thing that cannot be explained on the strength of this theory is the luxation of the lens, the lens being of ectodermal origin. It is his view, that a defective nutrition through the *arteria hyaloidea*, laid out from the mesoderm, conditions an impeded growth of the lens in relation to the rest of the bulb. A secondary luxation is a consequence of this. Bakker has shown on 4 lenses, which are extracted in cases of Marfan's syndrome, that these are always smaller than normally, and that they are more spheric. Their volume is equal to a stage of development in about the 7th month of foetal life. Weve takes this to be in favour of the congenital nature of the disease. In Weve's monography there is in no way any attempt to examine thoroughly the pathogenesis of the syndrome. His suppositions are only speculative, and no experimental proof of the correctness of his theories has been given. Against the theory of the congenital nature of the disease speak occasional observations of Ormond, Poynton and others (cit. Marfan), where the syndrome has developed in infancy after cases of infectious diseases.

Franceschetti, Vogt and others understand the disease as a mutation dependent on abnormal coupling processes of closely lying genera within the same chromosome. The mutations affect as well the mesodermal as ectodermal elements. By this the luxation of the lens is explained as a combined disturbance of two different seminal leaves. There are however, no certain points that can make this theory to more than an interesting hypothesis.

In conflict with the above theories are the attempts, that have been made to explain the syndrome as a disease of the ductless glands. The condition has been ascribed partly to a disturbance of the thyreoid gland, partly to the pituitary body, and it has also

been regarded as dependent on pluriglandular insufficiency. Common for these theories as for the others is, that the experimental proof is also here lacking. The theory of the pituitary body is especially supported by French authors, the anomaly by them being understood to be an «acromegaly arisen during the foetal period». This should be conditioned on an increased production of the growth hormone of the anterior lobe of the pituitary body in foetal life. Some authors claim to have shown an increase in the number of the eosinophil cells in pars anterior. As the pituitary bodies examined for a great part have been of children, where normally a relative preponderance of the eosinophil cells is found, these findings have not survived later criticism. Positive macroscopic changes of the pituitary body or increased size of sella turcica have not been reported. According to this theory the luxation of the lens is explained as an increased growth of the bulb of the eye in proportion to the lens, by which the suspensory ligaments of the lens break.

My three cases have not contributed to throw any further light on the condition. As the disease has been described only once before in Norwegian literature, these cases must be supposed to be of interest to illustrate the dominant heredity and the rich symptomatology of the syndrome. When the diagnosis has once been made, it will always be easy to recognize the anomaly. As regards the pathogenesis and the aethiology of the syndrome there is today much uncertainty, as none of the theories laid down are based on a sure foundation. The internal cause of the syndrome must be said to be entirely unknown at the present moment.

For permission to publish this material I am much indebted to my chief, dr. Ragnvald Bakke, Sandnessjøen.

### Summary.

Three cases of Marfan's syndrome, the father and two sons of a Norwegian fisher family, are here described. The elder son died in 1939 of pneumonia. The skeleton of all of them showed the typical symptoms of this disease, but only two of them suffered from a dislocation of the crystalline lens. This is the second publication from Norway relating to this rare syndrome, the cause of which must be considered completely unknown.

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(From the Medical Clinic, University Hospital, Uppsala, Sweden.  
Chief: Prof. G. Bergmark.).

## **Acute Thyrotoxic Encephalo- or Myopathy, its cause and treatment.**

By

**JAN. WALDENSTRÖM.**

(Submitted for publication November 17, 1944).

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During these last years we have observed several instances of severe thyrotoxicosis showing the type of symptoms that is usually classified as coma thyrotoxicum, thyrotoxic encephalopathy or myopathy. As the result of iodine therapy in large doses was very marked it seems appropriate to discuss these cases and their etiology somewhat more in detail. This type of thyrotoxicosis is usually regarded as very uncommon but it is at least not true for Uppsala, as we have observed 10 cases during a 10 years' period.

Before giving a description of our cases I shall try to summarize the present ideas about thyrotoxic myopathy and encephalopathy. At first view it seems obvious that these two groups of thyrotoxic disease ought to be kept apart. One type of thyrotoxic myopathy however: the acute form to be described here, is usually combined with cerebral symptoms and it is then impossible to make a distinction. Zondek has named these conditions coma basedowicum, but as the patients only develop coma in the very advanced stage and often lack the typical symptoms of Graves' disease such as exophthalmus and goitre it seems better not to use this term. It is possible that a new conception of the pathological mechanism in these cases will also give us a better name for all these conditions.



*Syndromes described in the literature as thyrotoxic myopathies.*

Russel Brain, certainly one of the best authorities on these questions, divides the thyrogenous muscular disorders into five groups, as follows:

1) *Chronic thyrotoxic myopathy* is a group characterized by the development of muscular wasting and weakness insidiously during the course of a thyrotoxicosis. The disorder is certainly extremely uncommon. The muscles of the thenar and the interossei are especially affected. Pareses of the larynx and the pharynx are sometimes found. There are never signs of pyramidal involvement and fibrillary twitchings are the rule.

The result of anatomical investigations of the muscles was rather poor. In one case published by Morgan & Williams it was completely negative, in another there were found foci with atrophic muscle fibres in the muscles gastrocnemius. In this case the result of the operation was excellent. The tendon reflexes may be diminished or lost. Prostigmin is of no use but treatment of the thyrotoxicosis may be followed by complete and lasting cure of the myopathy.

Parsons & Twort described a typical case in 1939. The patient was a man of 50, with the clinical picture of progressive muscular atrophy. No goitre, no tachycardia. Dalrymple's sign positive. He suffered from nervousness and tremor. The basal metabolism was somewhat increased. The myopathy was chiefly localized in the shoulders, the upper arms and the small muscles of the hand. The patient also suffered from an intermittent dysphagia with paresis of the muscles of deglutition. He was given a preoperative treatment with iodine. The operation was uneventful. Microscopical examination of the thyroid showed the typical picture of thyrotoxicosis. Three months after the partial thyroidectomy the musculature had a normal appearance. After six months the patient was working as before. It is to be regretted, that the influence of iodine treatment alone was not determined, but it is possible and even probable that restitution takes a long time in such chronic cases with considerable atrophy.

Morgan & Williams in 1940 published no less than four cases of thyrotoxicosis with severe chronic myopathy. Two patients were very much improved by thyroidectomy. One patient died during the preoperative treatment from respiratory paralysis. No obduction. The fourth had been operated upon only quite

recently. This important publication possibly shows, that such instances are not so rare as it is usually believed.

Ayer, Means & Lerman. Man 48 years old. Regarded as atrophía musculorum. In 7 weeks lost 24 pounds. Atrophy of practically all muscles with twitchings. Some exophthalmus and tremor. Very slight goitre. Moderate tachycardia. To the surprise of the author Basal metabolism + 58 %. Prompt response on iodine therapy. After 2 weeks treatment no twitchings. No cranial pareses. No degeneration reaction.

Starling, Darke, Hunt & Brain publish the history of a woman aged 60, who had suffered from asthenia for over a year. Then goitre with maximal exophthalmus and severe muscular atrophy (hands and pelvic girdle). Four months after the operation no signs of muscular atrophy.

It is however obviously very rare that such cases are recognized and it seems important to keep the possibility of thyrotoxic myopathy in mente in cases with a typical muscular dystrophies.

2) *Thyrotoxic myopathy with periodic paralysis* is certainly a very great rarity. Authors who are familiar with the picture have only been able to publish single instances. 4 cases from the files of the Mayo Clinic were published in 1931 by Dunlop & Kepler, but only one case was observed by the authors personally. The clinical picture is that typical for periodic paralysis but the complete disappearance of such attacks after the cure of the thyrotoxicosis seems to show what is the primary malady.

Most well known and the subject of intense discussion for several decades is the combination of 3) *myasthenia gravis and thyrotoxicosis*. All that has been written on this subject before the introduction of prostigmin for the treatment of the first malady is of limited value. It is certain that many cases suffering from thyrotoxic asthenia (which is not influenced by prostigmin) were formerly regarded as instances of myasthenia gravis. The favourable influence of prostigmin is one of the most important diagnostic criteria, but it must be remembered, that this drug may also cause temporary and partial relief in other types of muscular weakness (e.g. in amyotrophic lateral sclerosis). It is therefore important not to make the diagnosis myasthenia uncritically in all patients, who show some reaction to this treatment.

That there are found cases of typical thyrotoxicosis, who also suffer from real myasthenia is certain. Adler has published such a case with excellent effect of prostigmin. At the operation an increased thymus was not found. Six months after the operation there was still marked fatigability.

Hermann Zondek has published another case of typical true myasthenia, who reacted well on prostigmin and was considerably improved by radium treatment of the thymus. This was also a decidedly chronic case and did not resemble the acute thyrotoxic myopathy. Fraser has published a similar case who reacted well on prostigmin.

A fact that does not seem to have been discussed in the literature on the influence of hyperthyreosis on muscular metabolism is the connection between myotonia and hypothyreosis. The malady myotonia atrophicans may be accompanied by a low basal metabolism even if signs of classical myxedema are absent and no cure is obtained with thyroid hormone. French authors e.g. Mollaret and Sigwald quite recently described instances of muscular hypertrophy and a certain myotonic reaction in instances of hypothyreosis. The most striking feature was that the muscular symptoms disappeared with thyroid administration. Weitz has studied a case of postoperative myxedema with muscular hypertrophy even in the cranial muscles and spasms after sudden movements and when exposed to cold. The symptoms were not quite typical for myotonia but mostly resembled this malady. Thyroid therapy gave complete relief. Pancher & Woodward have investigated the case of a baby with muscular hypertrophy and signs of hypothyreosis. The child had a myotonic muscular reaction on percussion. Thyroid therapy gave complete relief but the symptoms recurred when the treatment was stopped. After 3 years of continuous treatment a complete cure was effected. These cases seem to have been very little discussed as illustrating the problem of muscular disorders and thyroid dysfunction from another side. It is possible that they are the reverse of hyperthyreosis with myasthenia viz. with muscular atrophy.

Weitz has published a very interesting observation. Physician 44 years old. Myxedema after roentgen treatment of thyrotoxic goitre. Basal met. -- 24 %. There developed a general muscular hypertrophy (even the lips, tongue and masseteres). The muscles became hard and the patient suffered from severe cramps espe-

cially in the cold and after sudden movement. Hardly any typical myotonia but repeated movements cause a certain improvement and mechanical stimuli may give a contraction. No tetany, no electrical myotonic reaction. Thyroid medication abolished all the muscular symptoms.

Since the work of Wolff and other American authors it seems to be an established fact that myasthenia and myotonia are to be regarded as reverse maladies. Quinine improves myotonia but aggravates the symptoms of myasthenia. The reverse is true of prostigmin. It is therefore an interesting fact if hypothyreosis may be accompanied by myotonia, where as hyperthyreosis is sometimes connected with myasthenia. The detailed mechanism of this thyroid influence on the transmission of the nerve impulse to the muscle is as yet not clear.

4) *Ophthalmoplegia exophthalmica* is the fourth muscular disorder often combined with thyrotoxicosis. Its clinical picture was outlined by Russel Brain, who analysed 31 new cases. It may sometimes arise after subtotal thyroidectomy, when the basal metabolic rate is normal or subnormal or the symptoms may develop during the course of a thyrotoxicosis.

As regards the etiology the authors seem to regard the exophthalmus as the primary change. From the experimental work in later years it seems to be an established fact that exophthalmus is caused by the thyreotropic pituitary hormone. Smelser has shown that it is possible to increase the weight of the orbital contents in guinea-pigs by the injection of this hormone. In thyroidectomized animals this exophthalmus is especially severe, a fact that fits in well with the cases, who develop a progressive exophthalmus after thyroidectomy or such cases of exophthalmic ophthalmoplegia, who show a low basal metabolism (Cf also Paulson 1937).

The rôle of this thyreotropic hormone for the development of Graves' disease and the importance of an antithyreotropic factor has been discussed by Loeser.

This has a mechanical influence on the extrinsic ocular muscles. The intrinsic muscles of the eye are never affected. The disease is eminently chronic. Prostigmin and iodine give no improvement. The condition may therefore be differentiated from the purely thyrotoxic myopathies and from myasthenia gravis.

The thyroid gland was examined by Turnbull in five of Brain's cases. In one there was found the typical picture of Graves' disease. In the other four, who had been healed with iodine there was found much colloid but the epithelium was often cylindrical and there were found numerous very small acini. Lymphocytic infiltration was also noted. Turnbull compares the findings with the picture from 50 consecutive cases of Graves' disease and concludes that the changes correspond to findings that are unusual in Graves' disease but they are not incompatible with this diagnosis. Extensive examination of several ocular muscles was only possible in Case I. There were found perivascular lymphorrhages in all five examined ocular muscles and in the m. sternohyoideus. The muscles have been examined in other cases also and have been found to be 3--8 times as great as normal with edema, round cell infiltration, and interstitial fibrosis but no fibrillary changes.

On the other hand it must be pointed out that one of Russel Brain's cases showed signs of chronic thyrotoxic myopathy together with ophthalmoplegia exophthalmica. The myopathy in this case was improved by thyroidectomy but some diplopia remained. The operation otherwise seems to have slight influence on the ophthalmoplegia. It is evident that the different types of thyrogenous myopathy may be combined in the same patient.

5) *Acute thyrotoxic myopathy* is regarded as very rare and Russel Brain points out, that death always occurs, usually within a week or two of the onset of the bulbar symptoms. This group will be the subject of the present paper.

It is usually associated with signs of thyrotoxic crisis or thyrotoxic coma and the most striking symptoms are those of a bulbar palsy. Muscular weakness of the limbs also occurs. Severe cerebral symptoms such as paraphasia, acalculia and psychosis with hallucinations seem to indicate that the disorder is often either accompanied (or caused?) by a real encephalopathy. It may be very difficult to determine if the palsies are of cerebral or muscular origin.

The following instances of acute thyrotoxic encephalo- or myopathy may be quoted from the literature.

*Summary of case histories from the literature of patients described as suffering from coma thyrotoxicum or thyrotoxic encephalopathy and papers treating this problem.*

Some older cases may be found in Sattler.

Friedrich von Müller (1894). Case I. Woman, 48 years old. Goitre, and numerous small lymph glands in the neck. Brown pigmentations in the face. Exophthalmus. Tremor. Nasal speech. Paretic dysphagia. Incontinence, somnolence. Exitus. The thyroid gland showed small acini, high epithelium and lymphocytic infiltrations. The medulla oblongata was carefully examined also by Siemerling. There was found a degeneration of nerve fibers in the vagus. Sympathetic system normal. A few recent bleedings in the nuclei nn VI, XI and X. Case II. Woman 22 years old. Typical Graves' disease with moderate goitre. Nasal speech with paretic dysphagia. After angina incontinence. Exitus. Spinal marrow, medulla oblongata, pons and pedunculi cerebri microscopically normal. Only in the bottom of the fourth ventricle rather numerous, quite recent, bleedings especially around the vagal nucleus. Sympathetic system normal. Case III. Woman. 36 years old. Slight exophthalmus, moderate goitre. Voice very feeble. Mentally clouded. Restless. Incontinent. Exitus. No microscopical examination. Case IV. Woman 48 years old. No typical encephalopathy but hallucinations. Marked orbital pigmentations. No obduction. Case V. Woman 25 years old. More chronic course of the disease. Strong exophthalmus. Severe perspiration. Brown pigmentations in the face. Fine tremor. Aphonia. Dysphagia paralytica. Later coma. Exitus. The medulla spinalis et oblongata, pons and pedunculi cerebri normal. Some small bleedings in the bottom of the fourth ventricle. Thyroid gland hyperplastic with numerous lymph glands. The author believes that the bleedings found in his 3 cases are agonal. Any signs of older bleedings or foci of any kinds were missing. The anatomist Siemerling examined the central nervous system.

Rankin (1896) Woman. «Bulbar paralysis». Exitus. Sutcliff (1898). Case V. Woman of 33. Nasal, feeble speech. Increasing vomiting. Muscles of pharynx and larynx paralyzed. Exitus with clear conscience.

Dinkler (1900). Woman of 42. Involuntary movements in the right arm, and both legs, later left-sided hemiparesis. Indistinct nasal speech «as in bulbar paralysis», incontinence, mental confusion, coma. Exitus. Oppenheim (1901). Youth of 16. A typical case with bulbar speech after exertions, ptosis, masticatory and palatal paresis. After 3 months exitus with new bulbar symptoms and cachexia. The malady ran a somewhat protracted course but cases with spontaneous recovery and relapse are known from later years. Nothing known about coma. Possibly an instance of myasthenia gravis. Klien (1909). Woman of 50. Very acute thyrotoxicosis with marked general asthenia, high fever, nasal, indistinct speech and palatal paresis 3 days ante exitum. Semicomatose. There was found a large thymus at the post mortem. Kappis (1911). The first case ought to be regarded as an instance of ophthalmoplegia exophth. Woman of 23. Palatal paresis with nasal voice. Ten months post op. still somewhat paretic. Woman of 46. Acute very severe Graves' disease with paretic dysphagia for several months. Exitus after

operation. The post mortem showed signs of degeneration in the nuclei nn. IX et X. Heuer (1916). Man of 23. Bilateral ptosis, diplopia, severe exophthalmus. Difficulty with the chewing, nasal speech and palatal paresis. For three weeks very feeble in the extremities. Mask-like face, open mouth, cannot cough. No sensory losses. Rather well nourished. No myasthenic electrical reaction. Death two days after arterial ligation in respiratory paralysis. Fischer (1922). Case XI. 35 M. Treated with roentgen. Restless and confused, later difficulty in swallowing. Exitus. Kessel & Hyman (1925). Seven cases died in a crisis before operation. Case II showed dysphagia, delirium, later coma. Was treated with 5 mg thyroxine i.v. with improvement. Three cases of crisis were treated with thyroxine with good result. «This therapy is to be regarded as a heroic measure in the presence of a fatal prognosis.» Klien (1927). Woman of 50. Fever, severe asthenia. Three days before death paresis of deglutition. Riese (1928). Gives the case history of a patient with postencephalitic parkinsonism, who developed a morbus Basedowi. With due regard paid to the common occurrence of these two maladies it is evident that their coincidence in the same patient may be purely fortuitous.

Wedd & Permar (1928). Woman 37 years. Typical exophthalmic goitre in 1914. In May 26th diplopia, exophthalmus and difficulties in moving the eyes. Loss of weight, firm goitre. Complete external ophthalmoplegia. Basal met.  $\div 22 - \div 44$  %. Blood pressure 130/65. The patient was given Lugol's solution with considerable improvement. Later paralytic dysphagia, incontinence. High fever, catalepsy. Delirious. Exitus in coma with tachycardia (230). Section: Thyroid gland: typical picture as in thyrotoxicosis. Microscopical examination of the cerebrum: nothing pathological. No signs of encephalitis. Goette (1929). Woman of 25. After roentgen treatment thyroid crisis with severe asthenia, blurred speech. Exitus. Typical Basedowic goitre and thymus persistens. Woman of 32. After roentgen treatment fever, leucocytosis, angina?, coarse tremor, blurred speech, incontinence. Later comatose with rising fever. Exitus. H. Zondek (1930). Four typical cases of Graves' disease: Woman of 32. Blood pressure 160/55. Fever, mental confusion. Pharynx dry. Severe incompensation. Coma. Exitus. Woman of 31. Subfebrile. Severe tachycardia. Coma. Exitus. Woman of 54. Temp.  $38^{\circ}$ . Severe adynamia, lower jaw hanging down. Pharynx dry, red. «Benommen». Real coma not present? Woman of 40. Speech blurred, paresis of deglutition, can hardly speak. With quinine and glucose improved. After seven weeks much improved. Prüfer (1931). Man of 33. «Apathetic». Exitus. Woman of 68. «Coma Basedowianum». Exitus. Woman of 49. Paresis of the arms, confusion. No detailed neurological analysis in any case. All developed after roentgen treatment. Wüllenweber (1931). Woman of 58. Enormous exophthalmus. Tremor. Tachycardia. Basal met.  $\div 70$ . Increasing mental dullness with bulbar speech and ptalism. Exitus. The central nervous system was examined by Spielmeyer, who found nothing pathological. Greene & Greene (1932). Point out that iodine therapy is the most important of all for the control of a thyrotoxic crisis. Relate one case of thyrotoxicosis, who suffered from varicose ulcers and was given injections for these in spite of warnings.

After (because of ??) this treatment a severe crisis with exitus. Carnot, Rudolf & Vèran (1932). Women of 29. Died in a coma after five weeks malady. Nothing about neurological symptoms. Müller and Livades (1933). Two cases (women of 55 and 31) with considerable mental dullness. Both were treated with potassium iodide (0,5 gx 2) with good results. Lahey (1932) writes a paper on atypical hyperthyroidism. He points out that «apathetic hyperthyroidism» occurs in patients over 40—50 years of age. Often no exophthalmus, goitre or tachycardia. The basal met. is usually not very much increased. These patients die in a coma, the «activated group» die in excitation. The apathetic patients are often undiagnosed, they get unexpected fatalities. No detailed case histories. Bayley (1934) has seen 51 instances of preoperative thyroid crisis. Gives the data of one iodine-withdrawal crisis (no coma). 19 of the cases died. It is important to know that the basal met. may be comparatively low. Insomnia is an early sign of impending crisis. Water and glucose together with iodine are very important in the treatment of such conditions. Digitalis gave no pulse decrease in any of the 51 cases. Krotoski (1934). Woman of 31. Strong exophthalmus. Tachycardia 8. Basal met. + 63. She developed signs of angina and became decidedly worse with blurred speech, apathia and intense asthenia. Paretic dysphagia, incontinence, coma. The patient was treated with Lugol's solution, but the dosage is not noted, and it is not quite clear if the improvement after a week was due to the treatment. She left the hospital and after 6 months she was in a rather good condition. After two months there were not found any signs of Graves' disease. Risak (1934) publishes some observations of morbus Basedowi in patients, who suffered from what was regarded as postencephalitic parkinsonism. Regarding these cases the same criticism holds true as for Riese's case. Only the fact that morbus Basedowi was significantly more common among patients with parkinsonism than among normals would be of any value as a proof. Wijnblad (1936). Case I. Man of 53. No exophthalmus, moderate goitre, tremor with athetoid movements. Later mental dullness, blurred speech, incontinence. Coma with fever (40°). Pulse 140 with auricular fibrillation (ecg.). Blood pressure 120/70. Was given enormous doses of iodine (up to 1700 mg/daily partly i.v.). Gradual improvement, operation. Complete cure. Control 2 years after op. Case II. Woman of 55. Very slight goitre. Tachycardia. Blood pressure 160/65. Basal met. + 55. Diarrhoea and vomiting. Precoma, confusion, blurred speech. Iodine i.v. (up to 760 mg/daily). Operation. Complete cure. Control 2 months after op. Case III. Woman of 37. Typical Graves' disease with goitre and exophthalmus. Blood pressure 160/75. Pulse 140, no fibrillation (ecg.). At first agitated. Later mental dullness. Right-sided VI and XII paresis, hoarseness, paretic dysphagia. Then coma with areflexia. In spite of iodine medication i.v. in large doses for 4 days exitus with extreme tachycardia, coma and hyperpyrexia (41°). Post mortem: diffuse toxic goitre. Central nervous system nothing pathological.

Friedmann & Kanzer (1937). Woman of 22. Relapse after operated Graves' disease. The patient developed a maniacal delirium. Was treated with 3 mg thyroxine i.v. The fever disappeared, so did the psychosis. After 6 weeks



coma, exitus. Post mortem: nothing of importance. The case history shows the progression of the disease from agitated to apathetic thyrotoxicosis.

Bansi (1939) has certainly the largest and most extensive experience of severe thyrotoxic crises (32 cases). As his work is published in a widely spread publication I shall not go into details and only refer to the original work. Of 30 cases, who were closely followed there were 19, who suffered from dysarthria and paretic dysphagia. One case had only dysarthria without symptoms from the pharynx. 24 patients were regarded as suffering from a coma. Only 2 of these were saved with iodine therapy. Practically all patients showed signs of adynamia. Incontinence, oliguria, albuminuria and urobilinuria were common. Terminal rise of fever was practically always present, but it is important to note, that in one case of typical mortal thyrotoxic crisis with coma and bulbar paralysis there was no final pyrexia. It is thus not an obligatory sign. It is also important, that the basal metabolism varied between very high values and such comparatively low findings as  $+30-40\%$ . Auricular fibrillation was only noted in 9 cases but it seems probable that it might have been present also in others.

Wolpers & Arnold (1941) have treated a number of cases suffering from thyrotoxic crises with diiodotyrosine (d.i.t.) intravenously. Case I. Woman of 36. At first great restlessness, later blurred speech, coma but normal temperature. Severe cardiac incompensation (fibrillation, liver enlarged). Treated with large doses d.i.t. intravenously. (1050 mg on four days  $+ 0.5$  g potassium iodide and 150 mg d.i.t. per os). Operation uneventful. Case II. Woman of 49. Classical Graves' disease. Adynamic, delirious. Great improvement with d.i.t. i. v. After the operation severe reaction, which was combated through the administration of 700 mg d.i.t. i.v. Good effect. Case III. Man of 46. Icteric, adynamic, somnolent. I.v. d.i.t. with good effect. Case IV. Man of 54. After angina blurred speech, severe diarrhoea, was given very large doses of d.i.t. i.v. (450 mg  $\times 1 \times 4$ ). Operation. Good effect. Case V. Woman of 52. Severely adynamic, mentally clouded. D.i.t. i.v. (450 mg  $\times 1 \times 4$ ). Good effect. Case VI. Man. After angina somnolence. Blurred speech and progressive adynamia. After four days of 400 mg d.i.t.  $\times 1 \times 4$  i.v. marked improvement. Operation. Good effect. Case VII. Woman of 28. Treated with prostigmin for «adynamic Basedow». No effect. Case VIII. Man of 53. Died in spite of very large doses of d.i.t.

Even if the clinical picture is varying, certain characteristic features may be pointed out. It is evident that a coma is often present perhaps always as an agonal sign. On the other hand the name coma Basedowicum is hardly suitable as many patients show other much more important symptoms than a coma as an indication of impending crisis. Some authors even regard insomnia as a warning (Bayley). The skin is often not so smooth and soft as usual but dry and hot. Pigmentations in the face of a dark-brown colour have been observed. The throat is often red and dry. This has certainly in some instances led to the assumption that an angina were the immediate cause of the condition. The status of the circulatory apparatus tends to aggravation with auricular fibrillation and low diastolic pressure. Sub finem there may be found an increased diastolic

pressure as sign of severe decompensation. (Bansi). Signs from the liver and the kidneys are not characteristic of an impending crisis but oliguria is a common result of the patients low fluid intake. That changes in the creatine-creatinine index may be helpful for the early recognition of a coma has been shown by Bansi. Bad appetite and great thirst are also said to be premonitory signs. A slight fever is such a common finding in thyrotoxicosis that it can hardly be of any diagnostic value but a rising fever without any apparent cause should always lead to the suspicion that a crisis is near at hand. In the final stages hyperpyrexia is a very common sign although it may be absent.

A number of cases published as thyrotoxic coma or crisis have not been investigated thoroughly as regards symptoms from the nervous system. (Gülzow, Schildknecht, Carnot a.o.). It is difficult to judge if localized pareses and other pathological signs would have been found in these cases. As the coma in itself may be regarded as a sign of disturbed cerebral function these cases have been included as instances of encephalopathy.

The bulbar symptoms are most characteristic. A pharyngeal paresis or paralysis with resulting dysphagia is common and often leads to severe disturbances. The speech becomes blurred, nasal, bulbar. Paresis of the vocal cords may lead to aphonia. But also the masticatory function and the movement of the eyes may become impaired. A very severe general asthenia is the rule and it may naturally be assumed that the paralytic muscles are only instances of the most profound adynamia i.e. that the same process is leading to muscular weakness of different degree. In such a case it may as well be assumed that this process is located in the muscles as in the central nervous system.

There are however other symptoms, whose location must be sought in the central nervous system such as paraphasia, acalculia, hallucinations and also such signs as choreatic or athetotic movements etc. It seems most appropriate to keep the old term encephalopathia for such instances and I shall later discuss the reasons, why also the term myopathy ought to be used for one group of symptoms.

As regards the anatomy of these conditions the data seem to be meagre. No biopsies of the asthenic muscles have been published nor do I know of any post-mortem examination of the skeletal muscles. The central nervous system has been examined thoroughly in a large number of cases. (F. v. Müller-Siemering, Wüllenweber-Spielmeyer, Klien, Kappis, Wijnblad-Behring a.o.). In some cases there were found bleedings in the region of the cranial nuclei. It seems probable that F. v. Müller is right in his judgment that they are hardly of any importance for the explanation of the syndrome and are rather to be regarded as agonal. He also points out that the brain has been found absolutely normal anatomically in typical cases. Since that time such an eminent authority on cerebral pathology as Spielmeier has been in a position to examine the cerebrum from one case and declares it normal. It is thus evident that the lesion is not anatomical but rather functional, a fact that goes well with the rapid effect of adequate therapy.

*Personal cases.*

*Case I.* A. A. Woman born in 1894. For about a year goitre. For half a year considerable loss of weight (8—10 kg) with diarrhoea. Tremor, amenorrhoea. Increasing heart troubles with severe dyspnoea.

Admitted on Nov. 4th 1935. Somewhat depressed, weeps during the conversation. Is not able to be still in bed and is always moving about. The skin moist. Eyes somewhat glassy with moderate exophthalmus. Fine and coarse tremor in the fingers. The respiratory movements quick, irregular «atactic» — very much resembling what is sometimes seen in patients with chorea. Some cyanosis of the lips and edema. Temperature subfebrile. Pulse 160. No angina. Thyroid gland diffusely enlarged. Measure of the neck 39 cm. Heart: some general enlargement; auricular fibrillation, pulse deficit 160/110; signs of hydrothorax, liver enlarged. Blood pressure 180—150/120. Reflexes normal. Urine: traces of albumin and urobilin. Treated with Verodigen probably with some effect as the tachycardia diminished and the pulse deficit disappeared. She also felt somewhat calmer and it was then possible to determine the B. M. which was + 47. viz. + 44 %. Ecg. auricular fibrillation with some ventricular E. S. On Nov. 20th rising, unexplained, temperature. No leucocytosis. The patient is now treated with roentgen. The basal met. went down with this treatment to + 25 %.

On Nov. 30th temperature increase to 39°, 8 with severe tachycardia. Signs of angina lacunaris. Leucocytes 9.900. On Dec. 3rd throat somewhat improved. Lower temperature. No signs of pneumonia but some expectoration. On Dec. 11th very nervous during the night. Talking incoherently. Small choreatic movements in hands and feet. Is not able to take a deep breath. Pulse 118/112. Blood pressure 155—140/85. During the following days severe asthenia. Is not able to put out the tongue. Definite paresis of N. VII. dx. The patient shows great difficulty in starting movements. No myodystonic reaction in the muscles of the right arm and hand.

During the following days severe mental symptoms. Is not able to answer questions correctly. Marked perseveration, is therefore not able to say the name of different objects directly. Very great difficulties in counting ( $2 \times 2 = 8$ ,  $2 \times 3 = 10$ ,  $4 \times 6 = 12$ ). Severe apraxia even for simple movements. Speech indistinct. Cranial nerves: no diplopia, paresis of right lower facialis, no pareses of the soft palate. The tongue now seems to deviate to the right. Great difficulty in opening the month. No achilles reflexes. On some days considerable excitement. Does not react when spoken to. Then comatose with great increase of the hyperkinetic symptoms from the arms and fingers (choreiform). On Nov. 11th exitus with temperature 41°, 8 and severe tachycardia. The post-mortem showed typical struma Basedowiana, bronchitis, thymus persistens (50 g), bronchopneumonia and splenitis.

The case historys show the typical development of an encephalopathia thyreotoxica. From the beginning only signs of hyperthyreosis. After angina typical severe symptoms. It is often discussed, if the thyrotoxic

crisis sometimes described as occurring after an angina is not really in itself the cause of the red, dry and sore throat. In this case it seems certain that an infectious process of the throat was really present. (Typical angina tonsillaris with crypts filled with pus, high fever, leucocytosis and increased sedimentation rate). Localized pareses were only noticed in the right facialis and possibly in the tongue, but there was severe general adynamia as sign of severe myopathy. The signs of cerebral dysfunction (encephalopathy) were unusually marked. The choreiform movements and the incoordination of the respiratory movements may well be regarded as indicating damage to the basal ganglia. The perseveration, the acalculia and the general psychotic symptoms ending in a coma indicate severe disturbance of the function of the cerebral cells. The possible mechanism of these symptoms will be discussed later.

*Case II.* G. L. Woman born in 1881. Admitted for Graves' disease. For three years increasing perspiration and tachycardia. Also noticed goitre. On Febr. 20th 1936 difficulties in speaking and paresis in the left arm. Bed-ridden since then. Admitted on April 25th 1936: Slight generalized swelling of the thyroid gland. Tachycardia. Basal met. + 25 %. Blood pressure 150/100. No tremor. Rather correct orientation but finds names with great difficulty. Is not able to give a coherent anamnesis. Cannot find the name of the month. Tells the order of the months correctly. No motorical speech defect. Finds the names of ordinary objects. All sorts of calculations quite inexact. Does not realize the difference between plus (+) and times ( $\times$ ), (used to do all sorts of calculations without pen and paper). No definite pareses, reflexes normal. On April 29th marked mental confusion. Is not able to read aloud. No initiative. When she has eaten one plate she does not by herself get along with the next. The same symptom is seen also in other practical occupations, washings etc.

On May 5th still more apathetic. On May 9th auricular fibrillation, severe tachycardia 140. Coma and rising temperature. Exitus on May 11th. The clinical diagnoses were cerebral arteriosclerosis (tumor??) + morbus Basedowi + bronchopneumonia.

The obduction disclosed inter alia: struma diffusa colloides et parenchymatosa toxica. Some parts of the gland showed a toxic picture with high epithelium. Microscopical examination of the cerebrum: leptomeningitis chronica.

The case history is typical for Graves' disease. Whether the insult accompanied by difficulties to speak and paresis of the left arm ought to be regarded as vascular, is impossible to judge. The post mortem at all events did not show any signs of haemorrhagia or thrombosis cerebri nor was any tumour found. Clinically a localized paresis does not belong to the typical picture of encephalopathia thyrotoxa. The difficulty to count (acalculia) without signs of real afasia have been described as a symptom of this disease (Aldenhoven). It was also noted in case I of the present series and I am inclined to regard this disturbance as not quite uncommon in thyrotoxic encephalopathia. The importance of the chronic leptomeningitis is not easy to evaluate. A lumbar puncture was not performed.

*Case III.* W. M. Man born in 1867. No previous maladies. Since the beginning of spring 1937 increasing dyspnoea, insomnia, bad appetite with considerable loss of weight. For about a fortnight vomiting after the meals. He had also had three to four loose motions daily. The patient had noticed an increasing tremor for about a year. He had been very nervous and suffered from severe sweating.

Admitted to the Med. Clin. on Jan. 5:th 1937 with the diagnosis *Insuff. cordis + Hypertonia*. Somewhat dyspnoic and cyanotic. Slight pitting edema of the ankles. Very nervous, severe tremor. Thyroid gland not palpable. Neck measurement 35 cm. Heart slightly enlarged to the left. Systolic murmur and frémissement; auricular fibrillation. Blood pressure 195/60. Capillary pulsations. Liver considerably enlarged. Urobilinuria. The patient was treated with digitalis and diuretics, without much benefit. A basal metabolic examination gave the value of + 62 %. He became restless at night and suffered from severe diarrhoea. The blood pressure showed the same big difference between syst. and diast. (200/90, 205/60, 195/55) on different days. The patient developed a coma with rising pulse (155) and temperature (39°, 3). Treatment with diiodotyrosine and quinine did not influence the development of the malady and the patient died in profound coma. The post mortem showed no signs of aortic insuff. but hypertrophy especially of the left ventricle and thrombosis auriculi cordis dx. Signs of general stasis, bronchopneumonia and acute splenitis. Micr. examination of the thyroid gland showed a struma colloides nodosa basedowificata (the slides could not be reexamined).

The clinical picture shows no localized nervous symptoms but the patient died in a coma with rise in pulse and temperature. Many of the cardinal clinical symptoms of thyrotoxicosis were present. The post mortem confirmed the clinical diagnosis. It is probable that an intense iodine treatment would have changed the fatal outcome.

*Case IV.* A. M. Woman born in 1871. For 7—8 years the patient has suffered from increasing dyspnoea on exertions, tachycardia and edema of the ankles. Has been treated durring the last year for hypertension. Digitalis did not give any relief. Since Oct. 1937 increasing symptoms with diarrhoea and cardial asthma. Bad appetite with enormous decrease of weight. (20 kg.). Insomnia.

Admitted to the Medical Clinic on Jan. 28th 1938 with the diagnosis *Insuff. cordis + albuminuria (uremia?)*. The patient looks very tired and emaciated, changes her place in bed restlessly and is never still for a moment. Gives adequate answers. Thyroid gland slightly enlarged. Fine tremor in the fingers. No exophthalmus. Heart: strong pulsation over the precordium. Ictus resistant. No frémissement. Systolic murmur. Auricular fibrillation, deficit 115/106. Blood pressure 220/100. Liver not enlarged. Albuminuria. Non protein nitrogen 33 mg %. Icterus index. (Meulengracht) 9. During the following days treated with digitalis without any improvement. Blood pressure 205/85, 250/90. Increasing leucocytosis.

A thyrotoxic crisis was suspected in spite of the fact, that the patient did not show any obvious enlargement of the thyroid gland nor a trace of exophthalmus. The basal metabolism was determined which gave the result  $+115$  (215 %). During the following days much worse with motorical restlessness, later coma. Temp. max.  $38^{\circ}$ . Increased temperature and pulse. It is to be regretted that no special search for pareses was made before the development of the coma.

5 ml Plummer's sol (= 630 mg J) were given i.v. in 300 ml 5 % glucose. On the following day unchanged status (it may be noted as a curiosity that the patient had a marked increase of the stippled erythrocytes after the injection).

During the following days considerable improvement. Eats and drinks very well. Is now able to take Plummer's solution per os.

The patient was transferred to the Surgical Department where a subtotal thyroidectomy was performed (Dr. Groth). The goitre was unexpectedly large as it extended down behind the trachea (50 g). Micr. diagnosis: struma colloides basedowificata. Signs of marked toxicity. Colloid: strong red colour with Kraus' staining.

Readmitted to the Med. Clin. on March 22nd. Very great improvement, no tremor, blood pressure 160/100 but still fibrillation. After her return home her hypertonia recurred. Pulse rhythm normal on ecg. from 10/5 1938. Readmitted on Nov. 17th 1939. Immediately after her return home she felt very well but she has now suffered from signs of cardiac incompenation. Heart: normal status, no fibrillation (ecg.). Blood pressure 195/130. Nervous system nothing important. Readmitted on Oct. 7th 1942. Felt rather well. No severe imcompensation. Increased 20 kg. in weight. After bodily exertion on. Oct. 10th the patient felt dizzy but did not lose consciousness. Increasing headache. On admittance cervical rigidity. Blood pressure 240/120. Lumbal puncture fluid macroscopically blood-tinged. After centrifugation strong yellow coloration. Protein reactions strongly positive. After some weeks diplopia with extrinsic and intrinsic paresis on the right side. Severe pains behind the right eye with occasional vomiting. Increasing ptosis with total paralysis of N. III. Nn. IV and VI normal. The patient was transferred to the Surgical Clinic for operation, if possible, of her carotid aneurysm. The operation could not be carried through as the patient got severe cerebral symptoms when the carotid artery was temporarily clamped.

Patient later died at home after a new subarachnoidal hemorrhage.

For many years severe incompenation regarded as hypertensive in its origin. The patient had not the classical face seen in Graves' disease and no palpable goitre, but showed the curious mixture of motorical restlessness and apathetic expression of the face. A coma developed rapidly. It was treated with large doses of iodine intravenously with considerable improvement. Operation with no complications. Good results of this treatment.

Case V. K. E. Man born in 1884. Previous maladies of no interes. At Christmas-time 1937 much work, overstrained, abdominal pains with vomiting and slight temperature. No appetite and increasing difficulty

in swallowing. Considerable loss of weight. Not been able to be out of bed for the last weeks because of dyspnoea, tachycardia and intense sense of fatigue.

Admitted on Jan. 8th 1938. Psychically quite clear but intensely fatigued. Is not able to sit during the pulmonary examination. Very feeble musculature. Thyroid gland normal. Blood pressure 120/70. Heart normal. Reflexes normal. Decided atrophy of the small muscles of the hand. Icterus index (Meulengracht) 10. A thyrotoxic crisis was suspected and an examination of the basal metabolism was performed. It gave the value + 44.

During the following days increase in pulse, leucocytes and temperature. Temp. max. 38°. Pulse max. 140. The patient became dull with periods of restlessness, no appetite, brings up great quantities of mucus but no real vomiting, no exophthalmus. Irregular tremor. He developed a transitory rightsided palatal paresis and later also signs of paresis of the pharynx (roentgen). Lumbar puncture normal. Blood pressure 110/60. Paroxysmal auricular fibrillation. From Jan. 18th—Jan. 21st. persistent fibrillation (ecg.). After three days' treatment with Plummer's solution 10 drops thrice daily the fibrillation disappeared. The pulse rate diminished. The general status improved. When the iodine medication was stopped the status got worse with increasing tremor and tachycardia and the auricular fibrillation started again. The patient was therefore transferred to the Surgical Department for operation.

Treated in the surgical department with Plummer's solution 15 dr  $\times$  3. On Febr. 28th subtotal thyroid resection (Prof. Hultén). The gland was larger than expected and very hard. The extirpated parts weighed 85 g. Macroscopically typical picture for Graves' disease. Microscopical diagnosis: struma Basedowi. The signs of toxicity were not so marked but the Kraus' coloration showed pathological changes in the colloid. After the operation the patient was treated with 5 ml Plummer's solution i.v. This was repeated once more on March 2nd. On March 9th oral therapy with iodine was stopped. Post-operative development uneventful with steady improvement. Ecg. normal. No tachycardia.

The patient suffered from atypical thyrotoxicosis. He showed intense asthenia with decided atrophy of the small muscles of the hand (chronic thyrotoxic myopathy). Later there developed signs of thyrotoxic crisis with mental dullness and pharyngeal pareses and also paroxysmal auricular fibrillation. A roentgen showed a typical picture of pharyngeal paresis. The patient has great difficulties in lifting the larynx. The morsel fills the sinus piriformes and valleculae. It enters the aditus laryngis. A streak is also seen in a main bronchus. When the pharynx is put under high internal pressure (Valsalva) it expands probably more than normally. With Plummer's solution perorally marked improvement. After operation completely restored.

In April 1944 (telephone information) the patient feels quite strong and works as usual.

*Case VI.* L. E. Woman born in 1876. Admitted to the Medical Clinic with the diagnosis myocarditis chronica (insuff. cordis), on June 28th 1939.

In Febr. 1939 vertigo. Dyspnoic on exertions for 10 to 20 years. The legs have also been swollen. She has had a bad appetite and lost much in weight since the spring of 1939. The last 10 days vomiting every day. Felt very tired. Previously no trouble with the stools. Now for some time diarrhoea every day. The patient has been treated with digitalis without success.

Status on June 28th 1939. Dyspnoic with slight pitting edema. Temperature  $37.7^{\circ}$ , pulse 100. Thyroid gland: right lobe slightly enlarged. Soft, with smooth surface, not tender. Heart: left border 13 cm, right 4—5 cm. Systolic thrill and bruit, most clearly audible over the pulmonalis. Slow fibrillation. (ecg). No deficit. Blood pressure 190/110. No albuminuria or urobilinuria. Non protein nitrogen 43 mg %. Basal metabolism = + 60 % on two different occasions. On July 9th vomiting. The general appearance resembles a severe thyrotoxicosis with dark brown pigmentations around the eyes and the peculiar motionless expression of the face probably caused by asthenia of the facial muscles. Eyes somewhat glassy, but absolutely no exophthalmus. Strong perspiration. The patient had passing *attacks* of Cheyne-Stokes' breathing. Pulse 90. Subfebrile. Is not able to eat by herself. Psychically not clear with obvious hallucinations, hears »the husband rumbling in the attics». Incontinent.

The patient was given Plummer's solution perorally but was not able to take it. She now developed a coma and was therefore given Plummer's solution intravenously 5 ml (= 63 mg J). together with 250 ml 5 % glucose for 3 consecutive days. With this therapy obvious improvement. Mentally quite clear. No Cheyne-Stokes' breathing. Pulse rate slower. Is able to drink but vomits after solid food. After a few days also able to eat. Body weight constant. On July 19th transferred to the Surgical Clinic. Basal metabolism still + 40 % but otherwise very much improved. On July 21st subtotal thyroidectomy (Kaijser). Anatomical diagnosis: Struma nodosa colloides basedowoides. The postoperative development showed no complications. Basal metabolism — 3 %. There was persistent auricular fibrillation and this was not regularised with quinidine. Very good increase in weight.

For a long time the patient was regarded as suffering from chronic myocardial failure. No exophthalmus or marked goitre. The expression of the face and the intense pigmentations around the eyes suggested a thyrotoxicosis. She developed a clear-cut psychosis with hallucinations. Was not able to eat by herself. Later incontinent and comatose. Iodine in large doses i.v. had good effect. Operation with good results.

27/4 1944. Is able to work as before her malady. Weight 80 kg. Thyroid gland not palpable. Blood pressure 210/160. Pulse irregular (fibrillation) with deficit 92/86. Is treated with digitalis in chronic doses.

*Case VII.* S. P. Woman born in 1900. In 1940 signs of »thyrotoxicosis?». Lost 10 kg in weight. Tired. Previous goitre has increased. Tremor. Dyspnoe. Menstruation normal. Admitted on Nov. 1st 1940. No symptoms from the eyes. Not nervous. Thyroid gland slightly enlarged. Blood pressure 135/80. Pulse 88. Urine normal. Basal metabolism + 12 % and + 20 %. Not regarded as definitely hyperthyreotic.

Readmitted on Nov. 18th 1942. No weight loss. The goitre has increased



considerably. Psychically very restless. Dyspnoe. Tachycardia. Menstruation normal. Not taken any iodine. On Nov. 13th very tired with pains in the chest and difficulties in swallowing. Is not able to eat or drink because of these symptoms. Speech nasal. Febrile (39°). Comes from the Otiatric Clinic for a paresis of the pharynx. The roentgen picture showed that the larynx is lifted when the patient is swallowing but the upper part of the oesophagus is hardly opened and the opaque meal passes slowly down the oesophagus. Pharyngeal paresis? On admittance very agitated. Incessant movements with the hands. Skin dry. Severe tremor. Tongue very dry. Thyroid gland enlarged, rather firm with smooth surface. Measure 34 cm. No exophthalmus. Eyes somewhat glassy. Heart not enlarged. Systolic bruit and thrill. Blood pressure 155/90. Liver somewhat enlarged. Urobilinuria. Slight paresis in right lower facialis? Pharyngeal paresis on the right side. All movements very feeble. Prostigmin without effect on the pareses. Reflexes normal.

The patient later suffered from an attack of tachycardia with pulse 140. Blood pressure 150/50. During the following time all food and fluids had to be given through a nasal catheter as it was impossible for the patient to swallow. The pulse rate increased steadily. Ecg. normal. The basal metabolism was + 67 %. The leucocytes increased to 16,700. The non protein nitrogen was 55 mg %. No albuminuria. On Nov. 22nd the general status had become much worse. The patient is semicomatose. Sleeps all the day. Sometimes very markedly flushed but no severe perspiration. The patient was treated through the catheter with Plummer's solution perorally but vomited.

On the following day she was given 5 ml Plummer's solution intravenously (= 630 mg J) in 300 ml 5 % glucose. On the following day no decided improvement. Is still sleeping all day. A new dose of Plummer's solution is therefore given intravenously. On Nov. 24th decided improvement, lower pulse and temperature.

Not so sleepy, moves spontaneously in bed. The pareses in the pharynx have improved, is able to expectorate some mucus.

On Nov. 25th transferred to the Surgical Clinic. Very much improved. 8900 w.b.c. Wishes to get out of bed. Is able to swallow fluids. After a week's treatment with Plummer's solution perorally the patient was able to eat without aid. Sometimes the food however passes down the wrong way. The patient has also had a passing paresis of convergence. On Dec. 7th operation (Prof. Hultén). Leftsided thyroidectomy, rightsided resection. Very little was left of the right lobe. The anatomical diagnosis was struma basedowiana. Marked toxical changes. Very little colloid, with Kraus' staining. After the operation the patient was able to swallow without difficulty. Movement of the palate very good.

The patient was retransferred to the Medical Clinic on Dec. 15th. General status excellent. No signs of thyrotoxicosis. Heart: systolic apical bruit. Blood pressure 120/65. Liver still slightly enlarged. Practically no palatal paresis but a typical *signe de rideau* is still seen. Urobilinuria still present. Basal metabolism — 14 %. When the patient swallows fluids

she sometimes gets a small amount into the nose if she sits upright but not if she leans slightly backwards. During the following time her condition improved steadily, and she gained considerably in weight.

Readmitted for control on March 9th 1943. Feels very well but has not started hard work. Practically all symptoms of thyrotoxicosis have disappeared. The patient sometimes feels more cold than previously. From status: Skin very dry. Is quite calm and well balanced. »Feels like another woman«. Has put on 7 kg in weight. Heart: no thrill. Soft systolic bruit. Bradycardia. Blood pressure 115/85. Liver not enlarged. Still some residues of the palatal pareses. No clinical signs of tetany. Calcium of the blood 9.4 mg %. Basal metabolism — 25 %. The patient was ordered thyreo-total medium 1 tabl. daily, and has since remained in perfect health.

Reexamined on May 3rd 1944. Feels fine. Weight 68 kg. Takes no tablets. No obvious symptoms of myxedema. Blood pressure 125/90. Pulse slow, regular. No subjective signs of palatal paresis but objectively there is found an assymmetrical position of the palatal arches and a marked *signe de rideau*. Roentgen: no signs of paresis.

This is a classical instance of encephalo-and(or) myopathy in Graves' disease. The nasal speech, the dysphagia with objective signs of pharyngeal paresis (roentgen), the general asthenia are quite typical. She developed a semicomatose condition with vomiting after food and drink which were therefore administered with the aid of a nasal catheter. I.v. administration of large doses of iodine had a very striking effect. After two days there was a decided improvement, the patient moves spontaneously, swallows better and expectorates. After a weeks treatment with Plummer's solution she is able to eat without difficulty. After operation the asthenia and pareses disappeared completely.

What seems most important is the fact that the general asthenia and dysphagia were rapidly improved and practically disappeared under treatment with iodine. This probably means that the derangement of iodine metabolism was the cause of the muscular symptoms. Some postoperative myxedema but otherwise healed.

*Case VIII.* E. O. Man born in 1877. Admitted on March 22nd 1941. During the autumn 1940 the patient lost appetite and felt tired. Very thin, weight 43.5 kg. Heart normal, blood pressure 165/100, considerable tremor regarded as senile. On admittance no enlargement of the heart. Tachycardia with fibrillation (ecg.) and great deficit (160/88.) Non protein nitrogen 97 mg %. Urobilinuria. Otherwise nothing abnormal from status. The basal metabolism was determined at + 74 %. and + 92 %. The blood pressure was found to be low, 120/80, and the auricular fibrillation continued even when the tachycardia decreased. Subfebrile. During treatment with digitalis, quinidine and diiodotyrosine 0.1 g  $\times$  2 the basal metabolism became normal and the weight increased 5 kg. Dismissed with chronic digitalis and d.i.t.

Readmitted on May 6th 1942. In the meantime he had made regular visits to the Med. Outpat. Dep. and continued with digitalis and diiodotyrosine. In the springtime he got worse and stopped his digitalis. Weight

50.4 kg. On admittance severely uncompensated with very rapid heart action, 168 and a pulse rate of only 61. Blood pressure 100/65. Thyroid gland hardly enlarged. Liver enlarged. Albuminuria. Basal metabolism + 12. (?) He feels depressed and nervous. No tremor, exophthalmus or diarrhoea. After a fortnight's treatment with digitalis and diiodotyrosine there was a rise in temperature. At first it was believed to be caused by pneumonia. The patient did not react well to sulphathiazol. Progressive mental dullness; does not eat and hardly answers when spoken to.

A thyrotoxic crisis was therefore suspected and *iodine was given i.v.* in large dose, Plummer sol. 5 ml., with 300 ml 5 % glucose. During the injection the patient gets more lively and answers adequately. After only one hour he is able to talk, eat and read the newspaper. He was given Plummer's solution 10 drops thrice daily and the improvement continued.

The patient was operated upon on June 10th. Subtotal thyroidectomy (Prof. Nyström). Microscopical diagnosis: struma colloides dysincratoria. The anatomical picture did not indicate a high degree of toxicity. The epithelial cells somewhat higher than normal colloid partly red after Kraus' coloration. Dismissed on June 19th. »Feels like another man». Readmitted to the Med. Clin. on July 6th, for treatment of his heart troubles. Suffers from paroxysmal thumping of the heart with severe dyspnoea and faintness. The heart showed considerable tachycardia with fibrillation (deficit 120/68). Liver considerably enlarged. Urobilinuria. Weight 53 kg. on admittance and 48.5 kg. after the edema had disappeared.

The patient was first treated with digitalis, which resulted in increased diuresis and loss of 4 kg. of edema fluid. He was given quinidine  $0.2 \times 2$ . On the following day normal rhythm. His rhythm remained regular during the following week and he was dismissed with quinidine  $0.1 \times 2$  on July 31st. Reexamined on Aug. 28th and Nov. 7th. No digitalis, nor quinidine. Normal rhythm. No signs of incompensation. Has increased about 10 kg. in weight.

Examined in the Medical Outpatients Department on Aug. 28th 1942. Weight 57 kg. No signs of incompensation. Ecg. sinus rhythm. On Nov. 11th not taken any quinidine for some time. Still normal rhythm (ecg.) Blood pressure 120/80.

Reexamined on March 31st, 1944. Weight 67.2 kg. Pulse rate regular (ecg.) »Feels fine.»

The patient suffered from a seemingly mild thyrotoxicosis for 2 years before a severe cardiac incompensation set in. After a rise of temperature and pulse there developed a coma. This was very quickly relieved with iodine and glucose i.v.

The very rapid effect seems to be especially striking in this case. This is perhaps most easily explained by assuming a direct action of the iodine in the periphery. It is to be regretted that signs of paresis were not sought before the coma developed.

*Case IX<sup>1</sup>.* E. W. Woman born in 1885. In 1936 nervous and depressed. In March 1941 »flu» with fever up to 39°. After this time considerable loss

<sup>1</sup> The case has been published by Rudström.

of weight in spite of a good appetite. About a month prior to admittance much worse with insomnia, tremor etc. Feeling of dryness in the throat. No paresis of deglutition. The patient was admitted on Nov. 8th 1941. She showed typical restlessness, tachycardia, fine tremor of the fingers but only slight rightsided exophthalmus. She had diarrhoea and fever. The thyroid gland was somewhat enlarged, rather hard. Fixed facial expression. Gait somewhat unsteady. Basal met.  $+ 50 \%$ . The patient was treated with diiodotyrosine  $0,1 \text{ g} \times 2$  with considerable improvement. Basal met. on Jan. 3rd 1942:  $+ 19 \%$ . After that time relapse with tachycardia, slight fever and restlessness. The basal met. increased to  $+ 53 \%$ .

The patient was transferred to the Surgical Clinic on Jan. 23rd 1942. The motionless face with its never-changing expression, the open mouth with ptyalism and the staring eyes strongly suggested an affection of the basal cerebral ganglia. The patient was lying immobile in bed and was not able to eat or to sit by herself. She seldom made spontaneous movements but there was considerable tremor in the hands. The speech was hard to understand, blurred and indistinct as it was. The patient had great difficulties to swallow. Psychically clear, no coma. Reflexes normal. Subfebrile temperature.

Treatment with Plummer's solution 10 drops thrice daily for 10 days before operation was instituted. This had a very decided influence on the temperature and pulse but the other symptoms remained unchanged. On Febr. 4th a subtotal thyroidectomy (Prof. Nyström) was performed. The histological examination showed a typical picture of Graves' disease.

The postoperative course was an eventful. During the next days after operation (the patient continued with the iodine treatment for 3 days increased to 20 drops  $\times 3$ , then for one day 10 drops ( $= 63 \text{ mg J}$ )  $\times 3$  after the operation) the general appearance of the patient changed considerably. The amimia disappeared. On the sixth day after operation she was able to sit in a chair. She has been controlled several times and her status has been normal. The changes in the expression of the face are beautifully illustrated on the three figures in Rudström's paper.

In this case the psychic condition was not so profoundly altered and there was no coma. The considerable asthenia with paresis of deglutition and low tone in the facial muscles (hanging jaw) and the general immobility of the patient make the diagnosis encephalopathia (myopathia?) acuta thyreotoxica certain. The result of iodine therapy was not so quick and striking as in some of the other cases but the dosage was much more restricted. Subtotal thyroidectomy had an excellent and lasting effect on the hyperthyreosis.

*Case X.* H. U. Woman born in 1870. Heart troubles for about five years. Treatment with digitalis without great benefit. On Dec. 30th 1943 the patient felt very hot during a journey in a train and on the following day she had severe diarrhoea and a temperature of  $39^\circ$ . No tencsmi. The diarrhoea stopped after two days. The patient has lost weight considerably for some time. Admitted on Jan. 3rd 1944, General status rather good but

Case	Age. Sex	Year	Goitre	Tremor	Exopht.	Vonitus	Diarrhoea	Weight loss	Basal metab.	Fever max.	Heart rate (Pulse rate)	Blood press.	Fibril- lation
I A. A.	41 W	1935	+	+	(+)	—	+	8—10 kg	+ 45	41.8°	160 (110)	150/95	+
II G. L.	55 W.	1936	(+)	—	?	—	—	?	+ 25	38°	140 (140)	150/100	+
III W. M.	69 M.	1937	—	+	—	+	+	+	+ 60	38.39°	90 (90)	205/60	+
IV A. M.	67 W.	1938	(+)	+	—	—	+	20 kg	+115	38°	122 (118)	250/90	+
V K. E.	54 M.	1938	—	+	—	—	—	++	+ 44	38°	140 (140)	110/60	+
VI L. E.	63 W.	1939	—	?	—	+	+	+	+ 60	38°	100 (100)	150/70	+
VII S. P.	40 W	1940	+	+	—	—	?	10 kg	+ 20	—	80 (80)	135/80	—
„	42	1942	++	++	—	+	?	—	+ 67	39°	140 (140)	150/50	—
VIII E. O.	64 M.	1941	—	+	—	—	—	+	+ 92	—	160 (90)	120/80	+
„	65	1942	—	—	—	—	—	—	+127	39°	168 (61)	100/65	+
IX E. W.	56 W	1941	(+)	+	—	—	—	15 kg	+ 52	39°	120 (90)	175/75	—
X H. U.	65 W	1944	(+)	+	—	—	—	+	+ 40	38°	180 (110)	130/80	+

Nervous symptoms	Iodine	Op.	Result
Paresis right lower facialis. General asthenia Apraxia. Severe acalculia. Dysarthria. Choreiform movements. Coma.	D. i. t. $0,1 \times 1 = 58$ mg J. $\times 1$	—	Exitus
Paresis left arm. Asthenia. Acalculia. Coma.	—	—	„
Coma.	D. i. t. $0,1 \times 1 = 58$ mg J. $\times 1$	—	„
Coma.	Pl. sol. 5 ml i. v. for 3 days = 630 mg J. $\times 1 \times 3$ . Then 15 dr. $\times 3 = 95$ mg J. $\times 3$ .	+	Excellent
Paresis N. IX dx. General asthenia. Semicoma.	Pl. sol. 15 dr. $\times 3 = 95$ mg J. $\times 3$ .	+	„
Hallucinations. Incontinence. Semicoma. —	Pl. sol 5 ml i. v. for 3 days = 630 mg J. $\times 1 \times 3$ . Then 10 dr. $\times 3 = 63$ mg J. $\times 3$ . —	+	„
Paresis N. VII dx. N. IX dx. Deglutition, paresis. Semicoma. —	Pl. sol. 5 ml i. v. for 3 days = 630 mg J. $\times 1 \times 3$ . Then 15 dr. $\times 3 = 95$ mg J. $\times 3$ . D. i. t. $0,1 \times 2 = 58$ mg J. $\times 2$ .	+	„
Semicoma.	D. i. t. $0,1 \times 1 = 58$ mg J. $\times 1$ . Later Pl. sol. 5 ml i. v. = 630 mg J. $\times 1$ and 10 dr. $\times 3 = 63$ mg J. $\times 3$ .	+	„
Blurred speech. Paresis of deglutition. Amimia. Cannot sit or eat. Mentally clear.	D. i. t. $0,1 \times 2 = 58$ mg J. $\times 2$ Then Pl. sol. 10 dr. $\times 3 = 63$ mg J. $\times 3 \times 3$ . Then 20 dr. $\times 3 \times 3 = 126$ mg J. $\times 3 \times 3$ .	+	„
Cannot speak nor use her hands. Semicoma.	Pl. sol. i. v. 2.5 ml. + 2.5 + 2.5 = 315 + 315 + 10 mg J. Later 15 dr. $\times 5 = 95$ mg. J. $\times 5$ .	+	„

D. i. t. = Diiodotyrosine.

J = Iodine.

Pl. sol. = Plummer's solution.

quite emaciated. Weight 43.8 kg. Slightly subfebrile. The thyroid shows a hard adenoma of the isthmus the size of a walnut. Considerable, coarse and irregular tremor of the hands and arms. No exophthalmus, no restlessness, no hyperkinesia when the patient is at rest, no evident pareses. Heart: no definite enlargement, auricular fibrillation (ecg.) with pulse deficit 120/90. Blood pressure 130/80. Urobilinuria but no albuminuria. Basal metabolism + 33 and + 44 on two different occasions. The patient ran a continuous fever about 38° and had a very high pulse rate (180/108, 170/140, 152/124 on different days). She was treated with injections of strophosid with no rapid or definite influence on the heart rate. On Jan. 7th the patient completely lost her faculty of speech. She was lying motionless in bed, was not able to eat by herself, but swallowed food, when she was fed. No other apparent neurological symptoms. About three years ago when the patient was treated in another hospital she developed an acute confusion which lasted for some time.

As the condition looked very grave, the patient was given large intravenous doses of iodine (2.5 ml Plummer's solution (= 315 mg J.). in 150 ml normal saline) on two consecutive days (Jan. 8th and 9th). On Jan. 10th she was given 0.8 ml Plummer's solution in the same dilution. After this treatment the pulse was 80/80 and a general improvement was noted. The patient was therefore given Plummer's solution per os 15 drops five times daily. The pulse rate was higher during the following week (about 100) but the pulse deficit was small. The fever disappeared and the general status was considerably improved. On Jan. 14th it is noted that the patient is able to give hesitating answers. Her status is rather changing but there is steady improvement from day to day. From Jan. 2nd the improvement is very marked. The patient is quite clear psychically. She is able to sit up in a chair, there is no marked tachycardia and no deficit. Her speech is still somewhat hesitating and a trifle «atactic». As this marked improvement started from the institution of iodine in large doses it seems probable that the cerebral symptoms also may have arisen from the thyrotoxicosis. The patient was transferred to the Surgical Clinic for operation. The patient was given Plummer's solution 15 dr  $\times$  5 for 2 days. On Jan. 24th operation (Prof. Hultén). (Subtotal resection of both thyroid lobes, weight 37 g). No postoperative reaction. Anatomical diagnosis: struma nodosa toxica. For about a week after the operation severe tachycardia with deficit. On Jan. 31st sudden drop in pulse rate with regular rhythm (ecg).

General status much improved. This is an instance of thyrotoxicosis with the chief symptoms from the circulation. Her mental status was rather uncharacteristic with absolute apathia and loss of initiative resembling a comatose condition. The effect of iodine therapy was striking and confirmed the diagnosis as did the microscopical examination of the thyroid gland and the postoperative disappearance of the auricular fibrillation.

### Clinical picture.

In all the 10 cases the diagnosis seems clear. As regards the patients who died without iodine therapy, the diagnosis may simply be based on the result of the post mortem. Also in the other cases the microscopical examination of the thyroid specimens from the operation showed unquestionable signs of thyrotoxicosis. (Professor Fåhreaus has been kind enough to reexamine the slides for which I offer my sincere thanks). In this connection it should perhaps be pointed out that the first 3 cases from the years 1935, 1936 and 1937 died. The seven cases from later years, who were treated after Wijnblad's publication in 1937 were saved. This is naturally a small material but the difference appears to be worth noting.

As regards the *age* of the patients none of them was below 40 and only two below 50. The age incidence is therefore rather high and much higher than that usually accepted in thyrotoxicosis. This is also apparent from the cases with crises in the literature, where no less than 17 out of 36 patients with data about their age (see survey of literature) were more than 45 years. On the other hand reports of quite a number of younger patients have also been published. In Bansi's material of 32 cases the age of the patients is not given and it is therefore not possible to use his material for such calculations.

In this connection it should perhaps be pointed out, that the common conception of Basedow's disease with large goitre and marked exophthalmus has done much to obscure the diagnosis of thyrotoxicosis in elderly persons. It is evident from my table, that a large goitre and marked exophthalmus were only exceptionally seen. I know of no data about the occurrence of exophthalmus and goitre among a large unselected material of thyrotoxicosis, where due regard was paid also to the atypical cases. It is evident from our own experience not only of encephalopathia thyreotoxica but also of thyrotoxicosis in general that their appearance is much less frequent in elderly patients. It seems as if the fact that atypical thyrotoxicosis is by no means rare among older patients, is growing more and more accepted in the literature. Bram (1940) found only 120 cases above 60 years in his material of 5000. This would give an incidence of 2,4 %. Cookson (1939) points out that many of the elderly patients have no exophthalmus. In his material of



400 cases 26 % belong to the biggest age group 50—60 and 15 % were 60—70 years old. Mathilde Fischer (1943) has published a study of »larvierte atypische Thyreotoxikose im Rückbildungsalter». She stresses the danger of missing the diagnosis in elderly patients. Eckerström has recently (1944) stressed the same points according to experiences from Gothenburg.

From the table page 22 it is evident that the other symptoms vary very much. Exophthalmus and goitre have already been discussed. Severe vomitings and diarrhoea are not uncommon and are probably of great significance. Weight loss during the time preceding the crisis is not always present and this goes well with the sometimes rather moderate increase in basal metabolism. This is an important fact as a slight increase in basal metabolism is often used as an argument against severe thyrotoxicosis. This discrepancy has also been noticed by other authors e.g. by Bansi. The importance of the basal metabolic rate for the diagnosis of thyrotoxicosis is sometimes overrated. Many authors have published cases of severe thyrotoxicosis with practically normal basal metabolism. One instance may be quoted from Curtis and as it was very closely analyzed. Case 18. Woman aged 44. She had a basal metabolism of + 11 with a greatly increased iodine output. Microscopic examination of the goitrous tissue confirmed the diagnosis. Slight fever is nearly always present but a terminal hyperpyrexia was only present in one of the three mortal cases in the present series: When the temperature has started to rise quickly even intense therapy is probably of no avail.

The question of the basal metabolism in uncompensated heart disease is not yet settled. It is quite undeniable that a severe dyspnoea must have a strong influence on the »resting» metabolism of the patient. Some authors are of the opinion that even in the absence of marked dyspnoea a number of cardiac patients with raised basal metabolism are found.

The symptoms from the *circulation* are naturally very important. Auricular fibrillation was present in all but two cases. (In one of these the sinus rhythm was not verified electrocardiographically). In the table the heart rate and the pulse rate are given for all cases where this was specially noticed. The blood pressure determination is usually regarded as being of great diagnostic importance. From case VII it is seen, that the first stage of the malady with only

signs of a mild thyrotoxicosis was accompanied by a normal blood and pulse pressure. Later, when the condition had become grave, the diastolic pressure was very low. In other cases the systolic blood pressure has been somewhat increased. Only one case showed decided hypotonia during stage with maximal pulse deficit, but then this sign remained after complete heart compensation.

The causes of the *neurological symptoms* will be discussed later, when the mechanism for the development of thyrotoxic coma is treated. In this connection it should perhaps be said, that the definition of a coma is rather vague. If only such cases, whose condition resembles a profound narcosis are regarded as instances of coma thyrotoxicum, this is certainly very rare and only seen a short time ante exitum. Many other cases in this material however have suffered from an absolute torpor with no initiative and slight reaction on ordinary stimuli. They have been termed instances of semicoma.

The signs of *bulbar paralysis* have been very marked in several cases and it is probable that they would have been noted also in other cases if they had been specially looked for. On the other hand I have seen cases in whom the general asthenia was so intense, that it was impossible to tell, whether they had any special pareses or not. It is evident from the literature as well as from my own experience that a paresis of deglutition is most common. The roentgenological picture of the pharynx has not been treated in the literature and I shall therefore give a description of the symptoms found in the roentgenological department (cases V and VII). Case V was only able to swallow the opaque meal, when he put his head forwards. When he had swallowed the morsel it gathered in the hypopharynx and filled the valleculae and sinus piriformes. After several trials it passed slowly down into the oesophagus. No hindrance for the passage through the oesophagus.

The paralytic dysphagia in cases of thyrotoxic encephalopathy does not seem to have been analyzed from a roentgenological point of view. Roentgen pictures were taken in two cases of obvious encephalopathy. The picture was very much the same in all instances as the patient showed inability to get the morsel down into the oesophagus. There were also found signs of an imperfect closure of the introitus laryngis. In cases V and VII the recessus piriformes were filled and parts of the opaque meal found its way into

the trachea. It is thus obvious that the coordination of the movements necessary for deglutition was severely impaired. The lifting of the larynx in case V was defective. The roentgenological picture cannot be differentiated from that seen in bulbar thrombosis, myasthenia gravis etc. but is quite unlike what is seen in the Plummer Vinson syndrome (dysphagia sideropenica), where the closure of the larynx and of the nasal cavity is always perfect. It is probable that the paresis of the lifters of the larynx which according to Laurell play a large part in the normal opening of the hypopharynx is one important factor in this type of dysphagia. That there may also be present a definite paresis of the pharyngeal wall may possibly be indicated by the distensibility of the pharynx on increased pressure.

The decidedly cranial localization of the pareses with impairment of deglutition, sometimes also paresis of the larynx, more rarely of the muscles innervated by the sixth, the seventh or the twelfth cranial nerves have made the diagnosis bulbar paralysis seem evident. It is not certain, however, that the process has really a central and not a peripheral location. Also in myasthenia gravis, now decidedly regarded as a disease of peripheral origin, the symptoms are most marked in the bulbar muscles. The craniocaudal gradient may give a plausible explanation of the predilection of the myasthenic process for the cranial muscles. It seems very probable that the same arguments may be used to explain the bulbar paralysis in thyrotoxicosis. A general adynamia is certainly the rule also in the muscles of the extremities and I know of no instances with isolated bulbar paresis without general asthenia. The very rapid (after some hours according to Bansi) change in muscle metabolism after the administration of iodine seems to speak in favour of a muscular process. This is manifested through disappearance of creatinuria and normalization of the creatine-creatinine index. We also know that the skeletal muscles contain considerable amounts of iodine. According to Veil one half of the total iodine content of the body is found in the skeletal muscles and only  $1/5$  in the normal thyroid gland. This also speaks in favour of the assumption, that iodine may be of importance for the normal function of the striated muscles even if we do not know anything about the state of muscular iodine.

On the other hand it cannot be denied that symptoms of un-

doubted cerebral origin may develop during any severe thyrotoxicosis. The general restlessness, insomnia etc. may be explained in several ways and is a well known symptom of thyroid overdosage. Also the tremor is a symptom of small value for localization. But such symptoms as definite choreiform movements as were observed in F. v. Müller's Case I and in my own Case I or athetosis as was noted in Wijnblad's case I are hardly to be explained otherwise than as being of central origin. Melkerson's studies of the positive myodystonic reaction in 2 out of 8 cases of thyrotoxicosis also indicate a central process with localization in the basal ganglia. Signs of extrapyramidal lesions have been found by Risak, although most of his cases are instances of postencephalitic parkinsonism, who later developed a thyrotoxicosis. His case I is probably an instance of thyrotoxic encephalopathy (See also Riese, Oppenheimer & Silver a.o.). Rudström has published the case history of Case IX in the present series as an instance of thyrotoxicosis with parkinsonism.

Such general symptoms as psychosis and coma are perhaps most easily explained as being signs of a generally deranged metabolism of the cerebral cells. Instances in which disturbances of psychical functions without certain signs of focal anatomical lesions were described and analyzed in some detail may be quoted. Bruns speaks about paraphasia in his patient in the beginning of a mortal thyrotoxic crisis. In two of my cases (I and II) there was noted a distinct difficulty to count and one of the patients, who was used to arithmetics in her daily work, had totally lost the sense of multiplication and addition. Aldenhoven has published a paper treating a case of thyrotoxic psychosis in which he explicitly remarks, that the patient was unable to count. On the fourth day after operation the signs of psychosis disappeared. A marked loss of initiative was also noted in several instances.

The psychotic symptoms in hyperthyreotics are usually described as maniacal and the classical picture is certainly that of extreme agitation. Lahey has formed the conception «apathetic» thyrotoxicosis in contradistinction to the usual «activated» type. The first form probably covers, what H. Zondek calls coma Basedowicum. It is remarkable that Lahey especially stresses the point that the apathetic form occurs in patients over 40—50 years of age. Exophthalmus is missing, the goitre is usually small, the

metabolism may be relatively little increased. Even without developing a profound *coma* these patients may show signs of lethargy with obvious hallucinations but without agitation. My Case VI heard her husband rumbling in the attic above her head and mumbled a conversation with her relatives, who were not at the hospital. After intravenous iodine treatment her confusion cleared up completely. The coma found in Case VIII also cleared up very quickly (some hours) after the injection of Plummer's solution intravenously.

These symptoms can hardly be regarded as anything but cerebral and the very prompt curative effect of iodine therapy seems to indicate, that they may be caused by a disturbance of iodine metabolism. Under such circumstances it is possible that some of the patients published as instances of Graves' disease of cerebral origin in reality are to be regarded as a more chronic form of encephalopathy caused by a deranged iodine metabolism.

Are there any facts that might indicate the importance of iodine for cerebral function? Analyses of different parts of the cerebrum in order to determine their content of iodine have been performed by Schittenhelm and Eisler. Their results at first sight seem to give a very clear picture of the situation. They could not however be confirmed by other authors. Elmer points out that the amount of material analyzed varied from 0,2—0,7 mg and the total iodine found was at most 1—2  $\gamma$ ! It is therefore obvious, that the determinations are completely unreliable and the fact that the authors have multiplied the value in order to get the amount of iodine per 100 g. must increase the errors considerably. The question of the iodine content in different parts of the cerebrum, e.g. in the tuber cinereum, is thus by no means solved. Many important problems are here awaiting their solution.

My cases definitely show that not only the general status of the patient and the circulatory incompensation may be improved with iodine as is well known from our everyday experience with patients suffering from Graves' disease. But there is also a prompt influence of large doses on the more specific symptoms of crisis. Not only the coma and the creatinuria, as has been pointed out by Bansi, Wijnblad and others, are strikingly improved with iodine medication, but I have also found (e.g. in Case VII), that the severe palatal paresis simulating a bulbar paralysis was practically

abolished after iodine treatment already before operation. This also holds true of several cerebral, probably cortical symptoms. The fact is of considerable importance for the discussion of the pathogenesis. On the other hand it should never lead to unnecessary postponement of the operation. These cases with their practically hopeless prognosis if left alone without treatment or if treated symptomatically with digitalis, glucose etc. are an excellent example of the necessity of treating patients with Graves' disease both medically and surgically.

I feel pretty sure that when we are able to make iodine determinations on blood and urine routinely, we shall find a large group of cases now labelled simply myocarditis and treated as such, who are instances of marked thyrotoxicosis and may be cured with iodine and thyroidectomy.

It seems tempting to ask, whether the good results that were probably sometimes seen in old times, when »arteriosclerosis» was treated with iodine, may not be explained in this manner. Among all these elderly people with incompensation there was probably a certain number, who were hyperthyreotic. Cases IV, VI and X, in this paper would probably have been regarded as instances of severe arteriosclerosis cerebri with cerebral symptoms and severe incompensation. If iodine had been given as a »resorbent» nobody with open eyes could have denied that the result was excellent! To me it seems quite natural, that in old times this drug was tried in all instances of what was regarded as one definite malady: arteriosclerosis. This reasoning may lead to a wholesome criticism also of our present conception of *ens morbi*: e.g. myocarditis (instead of pernicious anemia, iron deficiency, thyrotoxicosis), encephalitis (for thyrotoxicosis, acute porphyria, hypoglycemia) etc.

The influence of the thyroid gland on *muscle metabolism* has been investigated experimentally by a number of authors. One of the most important changes is an alteration in the excretion of *creatinine* brought about by thyroid dysfunction. The normal excretion of total creatinine (i.e. creatinine and the creatine that is sometimes found) in the urine is 1—2 g. In many cases of Graves' disease a low urinary creatinine has been found. More important than the determination of creatine and total creatinine is the fact that Graves' disease often leads to the appearance of creatine in the urine. It is evident that the formation of creatinine from

creatine is impaired. Under normal circumstances creatinuria is never found. The most important causes of creatinuria are fever, acidosis and some myopathies. It may be regarded as an established fact that the excretion of large amounts of creatine is a sign of deranged muscle metabolism.

Palmer in 1927 found very high values for »creatine» and he succeeded in bringing them down to normal with iodine medication. The amount of creatine in the urine was not parallel to the increase in metabolic rate.

Bansi has studied this problem in a large number of cases (32). He finds a rather good congruence between the degree of adynamia and of creatine excretion. He believes that the most important factor is the index  $\frac{\text{creatine.}}{\text{total creatinine}}$ . The highest normal value of this index should be 110 according to Bansi. Many typical and even severe cases without adynamia do not show any increase in the index. The cases however showing signs of impending coma usually have a high index. Bansi writes »it seems as if the excretion of creatine disappears completely or practically so with iodine medication». It must be assumed that the iodine has an influence on the peripheral creatine metabolism and in this way also on muscle metabolism. Bansi points out that not only this chemical change but also the clinical improvement may be very quick.

It thus seems as if it were possible to distinguish two groups of symptoms in severe instances of thyrotoxicosis. One group may be easily reproduced by overfeeding with thyroid substance or by the administration of thyroid hormone. Tachycardia with auricular fibrillation, increased metabolism with fever, restlessness, insomnia, diarrhoea, increased perspiration and in the severest forms an agitated delirium may be quoted. These symptoms are temporarily cured by the administration of small doses of iodine.

The other form is characterized by severe cerebral and muscular symptoms. The patients complain of intense muscular weakness, sometimes with loss of reflexes and definite pareses, usually of the cranial muscles, especially those of the pharynx. These symptoms often precede the very intense disturbance of cerebral functions. They sometimes have the type of an affection probably localized in the basal ganglia with choreiform movements, amimia etc. Severe damage to the psychic functions such as acalculia, paraphasia and

complete loss of initiative leads to a precomatose and finally comatose condition. But also other symptoms differ from the first type. The skin is usually dry, the tongue and throat red and dry and there is often oliguria and acetonuria. Still more important according to Bansi a.o. is the finding of a marked creatinuria. These symptoms seem to be very valuable as they are much more common and intense in cases of thyrotoxic crisis than in ordinary severe thyrotoxicosis.

### **Incidence, therapy, prognosis of spontaneous thyrotoxic crises.**

The incidence of so-called thyrotoxic crises of spontaneous or to put it more cautiously of non-postoperative type is judged very differently. Many authors regard them as a great rarity and this seems to be the opinion prevalent among most physicians. On the other hand Bansi who has of course had a very large experience (600 cases) of thyrotoxicosis has seen no less than 30 spontaneous crises in a comparatively short time.

From Denmark Krarup recently published a series of very interesting cases with what he calls spontaneous thyrotoxic crisis. Among more than 30,000 case histories from the Bispebjergs Hospital in 1932—42 there was only one case, where it had been possible to make the diagnosis thyrotoxic crisis. At a revision of the case histories there were found 3 instances of what must be regarded as a non-recognized mortal crisis. Against this is contrasted the occurrence of 5 such cases during the last half year.

With the exception of Krarup's interesting contribution, very little, if anything, seems to have been published in Scandinavia about this important question since Wijnblad wrote his excellent paper in 1937. Krarup's experiences and our own from Uppsala seem to show that this complication is by no means very rare and probably remains unrecognized in several cases. In one of the most modern and excellent textbooks on thyroid diseases (by Means and Richardson) the problem of the crisis is only regarded as postoperative. It therefore seems as if this important complication or rather result of the malady is not very common in North America.

If we ask the same question as Krarup: is this a new type of



thyrotoxicosis or not, I think that the incidence of the malady during the last 10 years in Uppsala may give an answer. During this time we have had about the same frequency i.e. in the mean one case yearly. This is probably very near to the real incidence of the severe disturbance in Uppsala as we have been on a sharp lookout for it under this period. But I think, that it is practically impossible to tell from old case histories whether there are other cases, who have been wrongly diagnosed. The difficulty is not to diagnose, that a patient with thyrotoxicosis gets a crisis but to recognise, that the patient is thyrotoxic and not only a case of e.g. myocarditis. I am quite convinced that under the diagnosis myocarditis + bronchopneumoniae (as an explanation of the premortal high fever and great prostration) many such cases are hidden. In the absence of exophthalmus and determinations of the basal metabolism it is only the general appearance of the patient and the unexplained high pulse pressure that might give a clue to a correct diagnosis. From my table it is evident, however, that this latter is by no means a constant sign.

For the therapy in such instances with severe thyrotoxic crisis only one remedy is of real value, namely iodine. It seems certain that the most important therapeutic rule is to give large doses. American authors have used doses exceeding one g of iodine daily and in a single dose they have given about half a gram. Wijnblad, who treated his cases with permanent intravenous drip has given still larger doses, in a few cases even 2,25 and 2,8 g pro die.

As regards the iodine dosage considerable confusion arises from the fact that what we call Plummer's and Lugol's solution have a different composition. Some workers, for instance Bansi, speak about American viz. German Lugol's solution. This further contains iodine 5,0, potassium iodide 10, aq. dest. ad 100. One ml (20 drops) contain 126,5 mg iodine. The German Lugol's solution is only one fifth of the American (Plummer's). One tablet of diiodotyrosine contains 58 mg iodine and is equivalent to 9 drops of Plummer's solution. One gram potassium iodide contains 0,764 g iodine. For intravenous injection several authors have given sodium iodine (Goetsch and Green). The problem has recently been treated by Krarup, who discusses the possibility of a deleterious action of potassium in such large doses on the heart. It is probable that it is best to reckon with this possibility and use sodium

iodide, when large doses are given. One gram sodium iodide contains 850 mg iodine.

It also seems evident that sufficient amounts of fluid and calories ought to be given to these patients in order to overcome as soon as possible their deficit in these respects.

As regards the prognosis this was always said to be practically desolate. Also authors with a large experience were of this opinion. Russel Brain (1939) points out that the outcome of acute thyrotoxic myopathy is always fatal.

Bansi (1939), who has by far the most extensive experience of spontaneous thyrotoxic crises has examined 24 patients with coma. Only two of these were saved with iodine therapy. «The therapy consists in early diagnosis» is certainly a paradox that holds true in this malady.

On the other hand some recent authors have a more optimistic outlook.

Krarup has (1943) published some very interesting observations on spontaneous thyrotoxic crises, where intravenous therapy with iodine had a favourable effect in 3 of the 5 cases. He is of the opinion that if a real coma has once developed there is hardly any chance to save the patient and he therefore stresses the importance of an early diagnosis.

Müller & Livades have seen two cases: one »schwer benommen», the other with »stark betrübles Bewusstsein». Both were considerably improved with potassium iodine.

Wijnbladh (1937) has seen two cases of spontaneous thyrotoxic coma, who were healed with large doses of iodine and consecutive operation.

Wolpers & Arnold (1941) have published five cases of coma or precoma, who were saved with large doses of diiodothyrosine intravenously and potassium iodide with consecutive operation.

But it must be remembered that very rare instances of healing with only iodine without a following operation have also been published. Most interesting is the observation described by Krotoski. Man of 38. Classical severe thyrotoxicosis. After angina blurred speech, severe asthenia, paresis of deglutition, incontinence, coma. After seven days' treatment with Lugol, improved. No operation as the condition was regarded as too grave. After two years completely healed!

Bansi gives the description of a spontaneous healing of a severe crisis. And it is not unique in the literature to find that the patients tell about similar attacks during earlier periods of their life.

### Iodine metabolism.

In order to understand the rapid effect of iodine in this condition it is necessary to discuss some fundamental points of iodine metabolism. That the thyroid gland contains an important part of body iodine has long been known. According to the analyses of Sturm & Buchholz (1928) the total body iodine varies between 20 and 50 mg. No less than one half of this amount is to be regarded as muscle iodine. Only one fifth belongs to the thyroid gland. One tenth is found in the skin and one seventeenth in the bone substance. Iodine is found in different forms. Veil (1927) has advanced the opinion, that iodine may be of great importance not only as a building material for the thyroxine but also be necessary as an ion. Zondek however thinks that it is present in such small amounts that it cannot have any other function than as a constituent of certain important active substances.

If inorganic iodine is administered to guinea pigs it is stored in practically all organs with the exception of the cerebellum, the liver, the spleen, the stomach and the uterus. Iodine is stored in the cerebrum, kidneys, muscles, abundantly in skin and hairs and especially in the lungs. From the lungs it is quickly lost and they are not to be regarded as a depot for iodine. Muscles, skin and skeleton are the chief depots according to v. Fellenberg.

If one lobe of the thyroid is extirpated and the animal thereafter receives iodine medication an analysis of the remaining lobe shows much higher iodine values than in the first resected one. It is probable that this iodine is chiefly present as diiodotyrosine and thyroxine.

Puppel & Curtis (1937) have shown that the urinary excretion of iodine rises very much subsequent to a total thyroidectomy. They regard this fact as a proof that there is a readily available supply of iodine in extrathyroid tissues. There must be a permanent extrathyroid store of iodine.

For the comprehension of iodine metabolism the recent work on radioactive iodine is of great importance. Hamilton and Soley

have made very interesting experiments in the determination of the iodine uptake in living thyroid glands. They record curves of the radiation from the thyroid gland during the hours following upon iodine medication in different clinical conditions. The uptake in thyrotoxicosis was very rapid but the gland was not able to retain the iodine. In normal persons the iodine accumulation was not so rapid but the iodine content remained constant for a long time.

Hertz, Roberts & Salter have made similar experiments on a large number of cases with Graves' disease. It is evident from their work that small doses of iodine ( $< 2$  mg) are retained in the thyroid nearly quantitatively (80—90 %). They also found that the thyrotoxic gland gives off its iodine very rapidly. Only a small part is excreted. The rest must be deposited outside the thyroid. It has not as yet been possible to locate it exactly. Another fact of the greatest importance for the understanding of iodine metabolism in Graves' disease is the difference between small and big doses of iodine. When small doses are given the thyroid gland has a very marked initial primata. Only if large doses are administered does the iodine find its way also to other organs.

The most extensive experiments with iodine balance were performed by Puppel & Curtis (1938). They had confirmed the results of previous investigators that patients with exophthalmic goitre show hyperiodemia and hyperioduria. In a series of balance experiments the patients were given a constant diet with low iodine content (average 29  $\gamma$ /day) for 5—6 days before the experimental period. 24-hour specimens of urine were collected for 3 days at a time. The iodine in urine, feces and even in the sweat was carefully determined. Iodine analyses were also carried out on samples of blood and on the food.

Three normal persons were studied for a period of 39 days. They had a negative iodine balance (average 43  $\gamma$ /day) on a low iodine intake. During 6 days of food abstinence there was probably some increase in the iodine losses. One of the normal persons was operated upon for a hernia and this gave a very strong temporary increase in iodine losses through the urine. After 6 days the balance was as before.

Five patients with thyrotoxicosis were examined. Three of them were kept on the diet with low iodine intake (about 87  $\gamma$ /3days). They lost considerably more (about 2 to 3 times) iodine than

normal persons, chiefly through the kidneys and the intestine. Two other thyrotoxic patients were given enough iodine to keep a normal person on a positive balance. Their balance however was negative. One patient was given 466  $\gamma$  but had a slightly negative balance (16  $\gamma$  per 3 day period). The next had an intake of 653  $\gamma$ . Her losses averaged 190  $\gamma$ . If iodine in large doses is given there results a strongly positive balance. This is still more marked in thyrotoxicosis than in normals. The more the iodine dosage (increase) the greater is the iodine retention.

The authors believe that the increased iodine excretion is caused by increased breakdown of thyroxine. It has been found that thyroxine does not leave the body in an undecomposed form. On the other hand Bøe & Elmer have shown that the urinary excretion of nonthyroxine iodine after the administration of thyroxine increases very much. Rest in bed, a diet rich in calories and calcium gave clinical improvement in one patient with Graves' disease and her iodine balance became normal. When she was given 10 mg iodine daily for nine days her basal metabolism went down and she retained much iodine. The iodine medication was then stopped for 39 days. Thereupon her iodine balance became strongly negative. It is therefore possible that this freshly administered iodine leaves the body more quickly.

It is a well established fact that the blood iodine in hyperthyroidism is usually increased and the thyroid iodine decreased. With iodine therapy there is a considerable rise in inorganic iodine and a contemporary decrease in organic iodine of the blood. This was shown in the important work of Johan Holst. He interprets these findings as indicating a tendency of the thyroid gland to retain its iodine when under the influence of an increased inorganic iodine content in the blood. The »diarrhoea of the thyroid gland», as Holst puts it, is thus changed to a retention. When the thyroid has been filled ad maximum, it is no longer able to retain any more hormone and therefore it overflows. The most favourable moment in the preoperative iodine treatment is then past. 18 days is according to Holst the mean time for optimal iodine effect but the individual differences are great.

Holst gives excellent descriptions of the effect of iodine treatment on the histological picture of the thyroid. Rienhoff made the first extensive histological examination based upon a comparison

of the picture from noniodinized and iodine treated exophthalmic goitres. His main results were the following. Very marked increase in the colloid. Increase in amount of fibrous tissue. Presence of small tumefactions resembling adenomata. Change in the epithelium from high columnar to flat cuboidal. Blood and lymph vessels markedly collapsed. The walls of the acini are no longer irregular in shape but smooth and even. Marked decrease in the number of mitotic figures. The article is illustrated with a number of excellent pictures. Holst points out however, that different pieces of the same goitre may show quite different pictures. In different small pieces of the same «primary toxic» goitre that were excised at the same time there may be found in one piece a normal picture in another typical changes and also intermediary pictures. Holst is therefore rather critical against Rienhoff's investigations when this author made excisions from the goitre before preoperative iodine treatment and compared the picture with the appearance of the thyroid at the operation. No case showed complete histological healing after Plummer's treatment according to Holst.

### The possible mechanism of spontaneous thyrotoxic crises.

Already Bier (1931) discusses the question of the iodine in the blood in cases with postoperative reactions in exophthalmic goitre. «Auf der Höhe der postoperativen Reaktion werden die niedrigsten Jodwerte gefunden. Wir müssen daher die postoperative Reaktion auf einem relativen Jodmangel beziehen». In summing up his ideas about these questions he writes: «Das Bild der Nachkrankheit glauben wir auf Grund obiger Untersuchungen berechtigt zu sein als hypothyroxämischen Shock zu deuten». This idea of the «hypothyrexemic shock» is taken over by Timpe and by H. Zondek in discussing the postoperative crisis.

In the preceding pages it has been pointed out that the effect of the iodine in spontaneous thyrotoxic coma may be very quick (see cases V and VI). Also Wijnblad (1937) stresses this momentary effect and discusses the possibility that it may not have anything to do with the secretion of the thyroid gland. The relevant changes may take place either directly in the blood or peripherically and the iodine may have something to do with tissue respiration. Wijnblad continues: The influence of the iodine seems to be

different in the two conditions: ordinary thyrotoxicosis with Plummer treatment and in crises with massive intravenous doses of iodine.

Bansi, who discusses the problem of spontaneous thyrotoxic crisis at a later date (1939), has no definite explanation of the symptom complex. He points out the possibility that also in the peripheral metabolism the iodine may normalize the glycogen metabolism. The possible influence of the thymus for the development of adynamia, severe toxic reactions and coma is the subject of a lengthy discussion. The parallel with Addison's disease and the rôle played by the suprarenals is also treated. As a summary he points out that the thyrotoxic coma develops in those patients, whose organism had been damaged by the influence of the »den Stoffwechsel erschüttenden Eigenschaften des Schilddrüsenhormons».

Wolpers & Arnold, who treated their cases with large doses of diiodotyrosine intravenously point out that it seems probable that an organism suffering from hyperthyreosis may be depleted of iodine from increased mobilisation and excretion, if the faculty to bind iodine is impaired especially in the time of a crisis.

Probably starting with the idea that the crisis is really a state of »hypothyroxemia» several authors have tried to treat it with thyroxine. Kessel & Hyman were the first to publish, what they regarded as positive results with this curious treatment. They claim to have improved three cases in this way. The patient published by Friedmann & Kanzer suffered from a maniacal delirium. After treatment with 3 mg thyroxine i.v. some improvement was found but the patient died six weeks later in a coma.

Is it possible with the aid of the previous discussion to make the picture clearer? What are the relevant facts?

1) The symptoms in a spontaneous<sup>1</sup> thyroid crisis (= the apathetic form of Lahey) cannot be provoked by thyroid over-dosage, which gives the agitated form instead. They cannot therefore be explained as simple hyperthyroidism.

2) The work of Puppel & Curtis has shown that a patient with thyrotoxicosis loses large amounts of iodine. The increased iodine metabolism must lead to a depletion of the iodine in the body

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<sup>1</sup> I do not enter on a discussion of the postoperative crisis and the possible identity of the two forms.

if the exogenous iodine intake is not very large. A case of impending thyroid crisis had the largest iodine losses ( $\frac{3}{4}$  mg daily).

3) The same authors have found that a simple operation (for a hernia) may lead to a temporary strongly negative iodine balance also in a normal person. Also after a complete thyroidectomy there is found a continuous increased iodine excretion in the urine. Operations of different kinds are known to precipitate a crisis.

4) The symptoms in a crisis are said to have been alleviated by the injection of thyroxine. This would be inexplicable if they were caused by hyperthyreosis.

5) From the work with labelled radioactive iodine we know that small doses of iodine are nearly quantitatively retained by the thyroid (Roberts, Hertz, Salter). Only when larger doses are given is an accumulation of iodine also found in other organs.

6) A thyroid crisis is not cured with the ordinary small doses of iodine necessary to control an ordinary thyrotoxicosis. The effect of large doses however is excellent.

7) The effect of iodine is very quick (Bansi compares it to the action of insulin in a diabetic coma). The muscle metabolism is regulated almost instantaneously as judged from the creatinuria. The pareses may be practically healed with only iodine medication already before operation (see the present case V and VII).

8) The muscles contain no less than  $\frac{1}{2}$  of the total body iodine. Also in some parts of the central nervous system there have been found considerable amounts of iodine. Points 5—8 seem to speak in favour of the hypothesis that the iodine has a peripheral action in instances of crisis.

I therefore think, that the following hypothesis gives the best and a rather complete explanation of all these facts. Hyperthyreosis has a tendency to lead to great losses of iodine. This iodine, chiefly excreted in the urine, is probably a result of thyroxine breakdown. If this were true increased hormone production should lead to increased losses of iodine. In some cases these are compensated. Then the clinical picture is dominated by the hyperthyreotic symptoms giving the agitated form of Lahey. In others there arises a lack of iodine, which causes the acute crisis or a more protracted apathetic form. The first form is cured by small doses of iodine. The importance of this treatment according to Holst's theory lies in the abolishment of "thyroid hormone diarrhoea". The second needs



large doses to fill the iodine losses in the tissues. A crisis may be precipitated by an infection or by any operation. These factors have been shown to cause increased iodine losses. The alleged favourable influence of thyroxine on a crisis may possibly be explained as an unspecific effect of any iodine-containing substance that may be broken down to iodine.

In every case of thyrotoxicosis there are, or, may develop symptoms of two or possibly three different kinds. One is purely hyperthyreotic, the other possibly iodopenic and the third may be assumed to arise from a hyperthyreotropic effect of the pituitary. In order to illustrate what I mean the following table may be of use.

<i>Hyperthyreotropic symptoms</i>	<i>Hyperthyreotic symptoms</i>	<i>Iodopenic symptoms</i>
Exophthalmus	Increased metabolic rate	Possible tendency to decrease in metabolic rate? (lower hormone production)
	Severe cardiovascular derangement	?
Large goitre	Goitre, large or small	Goitre often small, even absent.
	Subfebrile temperature	Terminal high fever common
	Agitation. Mania	Comatose viz. no initiative (apathetic).
	No paralyses	Asthenia, cranialpareses.
	Insomnia	Coma
	Tremor	Athetotic or choreatic movements.
	Therapy: small doses of iodine	Large doses of iodine
	Effect after some days	Sometimes immediate effect.

It is evident that all these symptoms might develop to a different degree in different patients.

### Summary.

The author gives the case histories of 10 patients showing the picture of so-called spontaneous thyrotoxic crises (thyrotoxic encephalo- and myopathy) from the last 10 years in the Medical Clinic, Uppsala. The first 3 cases died. The last seven, who were all treated with large doses of iodine, recovered after operation.

Some clinical data, above all the very rapid effect of large doses of iodine, are discussed.

The difference between the purely hyperthyreotic symptoms that may be produced by thyroid overfeeding and a number of symptoms seen in spontaneous thyrotoxic crises is stressed.

Some important facts in iodine metabolism are discussed, above all the results of metabolic experiments with radioactive iodine and the balance experiments of Puppel & Curtis. It is evident that thyrotoxicosis might lead to severe iodine losses and the possibility of a depletion of the iodine depots is pointed out.

The fact that no less than half the total iodine in the body is found in the muscles and only one fifth in the thyroid, illustrates the importance of extrathyroid iodine. It seems possible that the very rapid effect of large doses of iodine on the symptoms of acute thyrotoxic myopathy may be explained as a correction of an iodine deficiency in the periphery.

It is possible that cases of severe thyrotoxicosis may show combined symptoms of hyperthyreosis and iodine deficiency and that the spontaneous thyroid crisis is chiefly caused by a lack of iodine. If this is true the importance of iodine medication in sufficient doses must be remembered and iodine will be as necessary in the future even if hyperthyreotic symptoms may be treated with thiocarbamidum or similar compounds.

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From the Medical Department of the Præsto County Hospital, Næstved,  
Denmark (Chief-physician: S. A. Holboll, M.D.).

## Case of intermittent branch block in a patient with myasthenia gravis.

By

VAGN BAARK.

(Submitted for publication February 20, 1945).

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In 1944, a woman, 51 years old, entered this hospital with two rather rare lesions: myasthenia gravis and intermittent branch block.

In recent years attention has been called to the occurrence of cardiovascular abnormalities in myasthenia gravis, and we have tried, therefore, to ascertain whether the branch block in this patient might have primary connection with her myasthenia — whether it might be a part of the syndrome of myasthenia cordis.

### *Case History.*

The patient is a woman, aged 51, who has never had scarlet fever, diphtheria or rheumatic fever. The menses have been irregular since March 1943. She has now climacteric symptoms in the form of hot flushes to the head; no palpitation of the heart. She has always been in good health until about a year ago when she commenced complaining of tiredness and muscular weakness, especially in the arms, head and neck, but this condition varied a good deal.

10 days before admission, however, her condition was aggravated markedly, and she became so tired that she had to keep to her bed. She was unable to raise her head from the pillow, her muscular power was at its best in the morning, poorest in the evening. She further complained of difficulty in swallowing (what she drank went the wrong way); and chewing her food made her tired. In the past year she has lost about 15 kg in weight. She also has difficulty in speaking (she cannot say anything for tiredness).

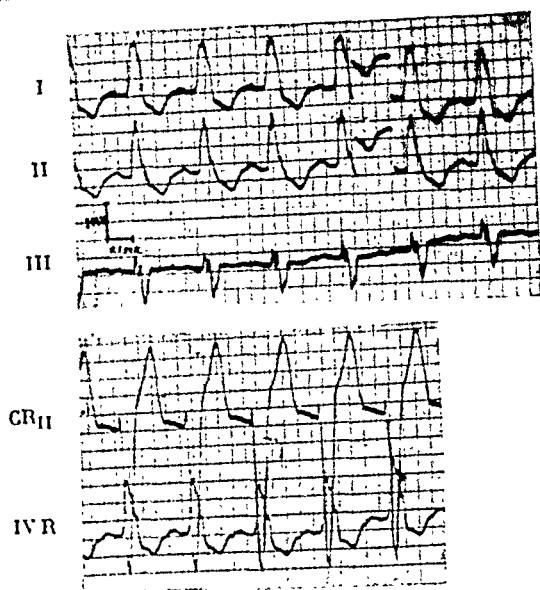


Fig. 1.<sup>1</sup> Electrocardiogram taken on 21/6/44: Action regular. P waves normal. PQ: 0.13 sec. QRS: 0.13 sec.  $R_1$  and  $S_3$  large and notched.  $T_1$  and  $T_2$  negative;  $T_3$  low positive. CR<sub>II</sub> shows a low R wave, a deep, broad negative S wave, and a positive T wave; ST elevated. IVR shows a broad positive R wave, negative T wave, and lowered ST.

*Ophthalmoscopy:* Normal findings.

*Fasting Blood Sugar:* 84 mg %. Glucose tolerance test (70 g glucose by mouth): Max. blood sugar 167 mg %; duration to initial level (85 mg %) 2  $\frac{3}{4}$  hours.

*Creatine Output in Urine:* 160 mg in 24 hours.

*Standard Metabolism:* 120 %; 124 %.

As to pulse and electrocardiography, see below.

### Clinical Remarks.

The diagnosis myasthenia gravis is established by the characteristic symptoms: Ptosis of the eyelids, universal muscular impairment localized especially to the muscles of the cranium, dysphagia, diplopia, and especially the prompt effect of prostigmin. This lesion appears to have developed together with the appearance of the climacterium. This is in keeping with previous observations on the influence of menstruation and pregnancy on the condition

<sup>1</sup> 1 cm = 1 MV. as ordinate, and 1/10 sec. as abscissa — in all the leads.

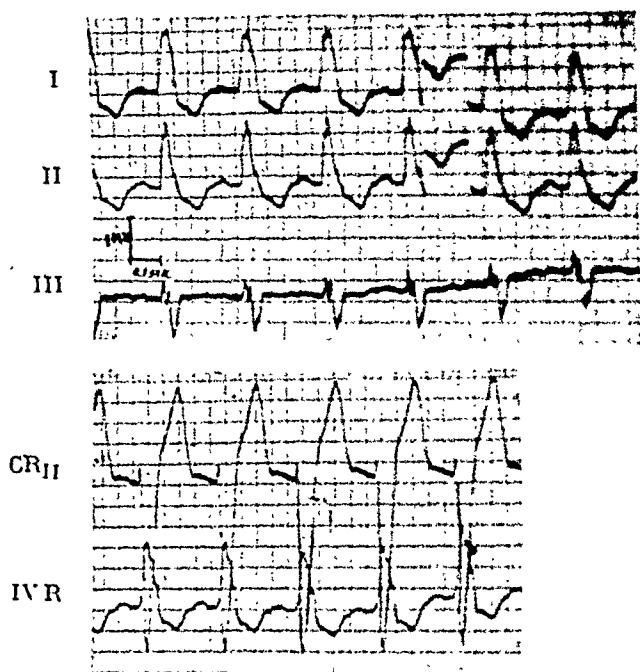


Fig. 1.<sup>1</sup> Electrocardiogram taken on 21/6/44: Action regular. P waves normal. PQ: 0.13 sec. QRS: 0.13 sec. R<sub>1</sub> and S<sub>2</sub> large and notched. T<sub>1</sub> and T<sub>2</sub> negative; T<sub>3</sub> low positive. CR<sub>11</sub> shows a low R wave, a deep, broad negative S wave, and a positive T wave; ST elevated. IV R shows a broad positive R wave, negative T wave, and lowered ST.

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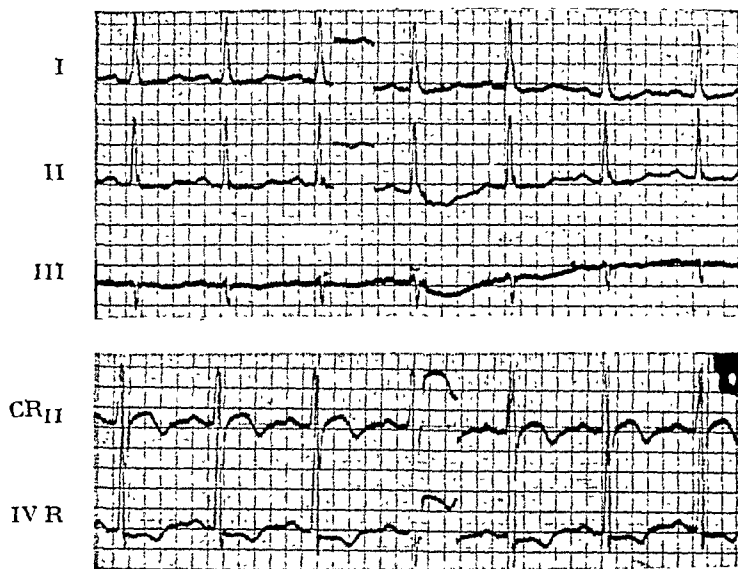


Fig. 2. Electrocardiogram taken on 23/6/44: Action regular. P waves normal. PQ: 0.13 sec. QRS: 0.06 sec.  $R_1$  and  $S_1$  large, not notched,  $ST_1$  and  $ST_2$  lowered 2 mm below the isoelectric line.  $ST_3$  normal.  $T_1$  and  $T_2$  positive.  $CR_{II}$  shows a positive initial deflection; ST elevated 0.3 mm; T negative.  $IV R$  shows a positive initial deflection: ST lowered 0.3 mm; T negative.

of patients with myasthenia gravis [Viets & Schwab (14)]. This case must be considered rather serious as even large doses of prostigmin failed to make the patient quite symptom-free.

**Electrocardiography.** One of the most interesting features presented by this patient is the electrocardiogram which keeps alternating between the two main types, shown in Figs. 1 and 2.

Fig. 1 shows a typical left-sided branch block with opposite deflection of QRS in leads I and III [discordant type, Pardee (12)]. The conduction time is not shortened. Here then, we are not dealing with the branch block described by Wolff, Parkinson & White — the so-called WPW block with short conduction time.

Fig. 2 presents no sign of branch block; and in the following this would be designated as the «normal type». It is not quite free from pathological changes, however, as ST is lowered a little in leads I and II, and the precordial leads give negative T waves.

While one main type, the branch block, keeps showing the same form for months, the normal type is subject to variation — as shown in Fig. 3.

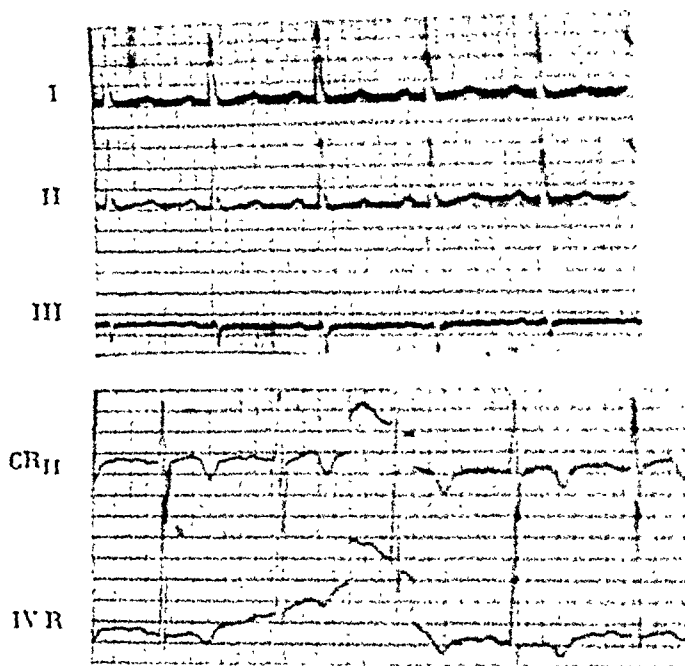


Fig. 3. Electrocardiogram taken on 14/7/44: No shift of the ST segment in the extremity leads or in CR<sub>II</sub>. In IV<sub>R</sub> the conditions are uncertain. T<sub>1</sub> and T<sub>2</sub> a little higher positive. In the precordial leads the T waves are still negative.

In Fig. 3, taken on 14/7, the changes in ST are gone, and the positive T waves in the extremity leads are higher. For several months then the ST segments keep constant, while the T waves vary, being sometimes positive, sometimes negative. Thus they are often negative after the branch block has persisted for some length of time.

So this patient is suffering from intermittent branch block (paroxysmal bundle-branch block), a relatively rare lesion. Still, with the more frequent employment of electrocardiography nowadays it is encountered more frequently.

Comeau *et al* (3) have examined 13 cases and collected 58 from the literature, finding the following features: The lesion is more frequent on the left side. In most of the cases an organic lesion is found as a basis for the electrocardiographic changes, in sequels after the frequency: coronary sclerosis, chronic rheumatic heart lesion, diphtheria and thyrotoxicosis. The presence of the block depends primarily on the condition of the myocardium, secondarily



on the rate of the heart beat. Thus it is practicable in some cases to abolish the branch block by artificial decrease in the rate — for instance, by pressure on the carotid sinus or in the bulb of the eye — as the affected conduction bundle thus is better enabled to recover between the impulses. But there is no established relation between the presence of the branch block and the frequency, as the capacity for conduction varies.

Stenström (11) found that pressure on the vagus in every instance lowered the frequency and in some cases abolished the block. The dependence of the branch block on the frequency has been demonstrated also by Donath (4) who in one case of intermittent branch block was able to elicit the branch block after injection of euphyllin, which increases the frequency. In another case he produced the branch block through the dilating effect of euphyllin on the coronary vessels.

Most of the cases of branch block reported in the literature have had an organic basis, usually corresponding to a serious heart lesion. More recently, however, studies on the influence of the vegetative nervous system on the electrocardiogram have shown that branch block may arise also as a functional phenomenon.

In one patient with hypertension and coronary affection Co-meau was able by pressure on the vagus to elicit the branch block without any changes in the frequency.

In a man with paroxysmal tachycardia Purks (13) was able by pressure on the left carotid to produce branch block in three complexes without any change in the heart rate. Holzmann (6) has reported the case of a patient with bovine heart and pronounced impairment of the myocardium in which there was a branch block corresponding to the bradycardial phase of the respiratory arrhythmia.

Lind (8) has described a case without anamnestic or clinical evidence of any organic heart lesion in which the electrocardiogram was normal when the vagus tonus was low, whereas it showed several changes, including »branch block-like complexes» when the vagus tonus was high.

The most natural explanation of these incidences of branch block is that they are due to a direct action of the vagus on the conduction bundle, with inhibition of the conductivity. The effect is of functional character and may be seen in cases without any signs of a serious heart lesion.



Fig. 4. Electrocardiogram A was taken immediately before intravenous injection of 5 cm<sup>3</sup> of euphyllin. Rate: 70.

B was taken 45 sec. after the injection. Rate: 100.

It will be noticed how the electrocardiogram discontinuously reverts from the normal type to branch block, at ↓.

As far as I have been able to find out intermittent branch block has not been observed previously in myasthenia gravis. On the other hand, on examination of 11 patients with myasthenia gravis Ask Upmark (2) found cardiovascular anomalies in most of them, especially in the form of tachycardia, dyspnea and certain changes in the electrocardiogram. Sometimes the peripheral circulation was affected — as evident from cold, damp, cyanotic hands, the so-called «reptile hands». It was characteristic of all these symptoms that, like the other myasthenic symptoms, they were abolished by prostigmin. Electrocardiographic changes were found in 4 of these patients, consisting in depression of ST<sub>2</sub> and small low T<sub>1</sub> and T<sub>2</sub>.

Correspondingly, in 2 cases of myasthenia gravis Oettel (10) found a depression of the ST segment, in one case in leads II and III, in the other in all three extremity leads. In these cases too, the electrocardiograms were normal after treatment with prostigmin.

As our patient entered the hospital with branch block (Fig. 1)

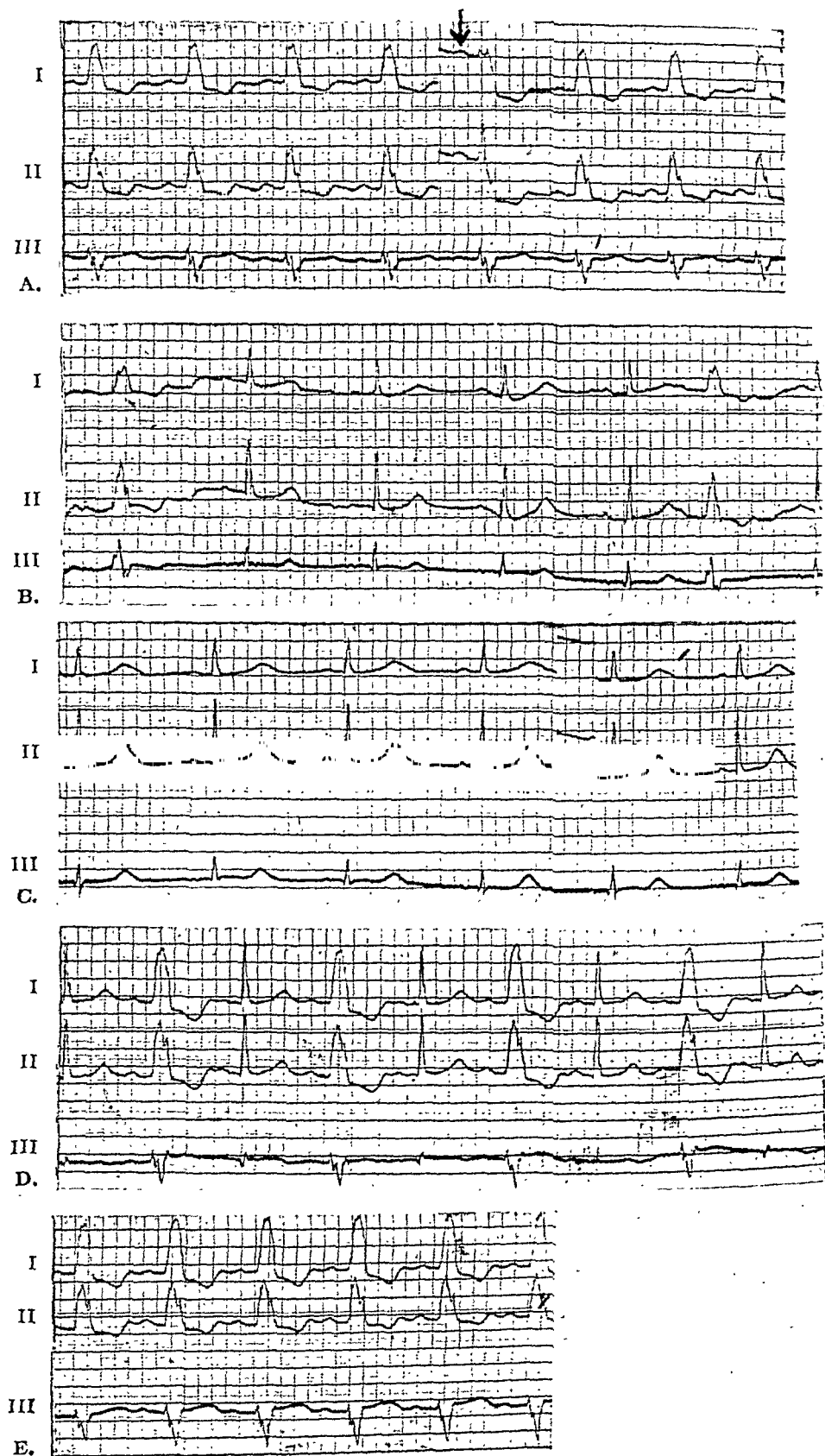


Fig. 5. Electrocardiogram A (branch block) was taken un-  
 1 cm<sup>3</sup> acetyl cholin, subcutaneously (at ↓). There was a  
 with nausea, vasodilatation and sweating.

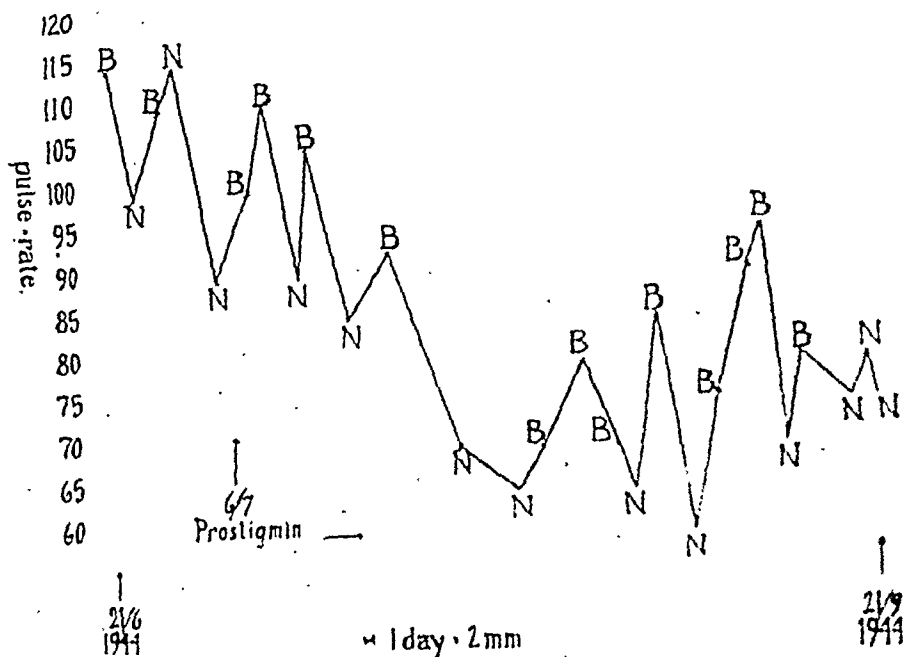


Fig. 6. Graphical presentation of electrocardiograms taken fairly frequently through a period of 3 months.

B: Branch block. N: Electrocardiogram of normal type.

At first the pulse rate is high, but about two weeks after the institution of continual prostigmin therapy (on 6/7) it falls to a lower level.

and after a few days' treatment with prostigmin — altogether 8 tablets of 15 mg — showed an electrocardiogram of normal type (Fig. 2), it was at first believed that the branch block was due to the myasthenia. After discontinuance of prostigmin, on the day following the reappearance of the branch block an intravenous injection of prostigmin was given in order to try its direct effect on the heart. The branch block was then found not to disappear in

(Fig. 5.)

B was taken 2 min. after the injection. Now the electrocardiogram is of normal type, with a few branch block complexes (with P waves). Rate: 67.

C was taken 5 min. after the injection. Now the electrocardiogram is of entirely normal type, with a rate of 62. All the T waves are high, positive.

D was taken 30 min. after the injection. Now the rate has increased to 92. Every other complex is seen to be of normal type, every other of branch block type, the so-called intermittent 2:1 branch block. Now, then, the rate is of such a magnitude that the blocked branch of His-Tawara's bundle is able to recover for the conduction of every other impulse.

E was taken 45 min. after the injection. Now the rate is 95, and the electrocardiogram shows a clear-cut branch block.

spite of injection of 1 cm<sup>3</sup> prostigmin (0.5 mg). The branch block turned up and disappeared apparently independently of the treatment with prostigmin. Nor was prostigmin able to change the normal type of heart action to branch block on intravenous injection of 0.5 mg. The heart rate is not altered by these injections of prostigmin.

In tests with pressure of the carotid sinus and on the eye bulb no change is seen in electrocardiogram; in particular, the heart rate is not altered. This is in keeping with previous observations [Foxe, Salomon and others, cited after Ask Upmark (2)] to the effect that the oculocardiac reflex is abolished in myasthenia gravis.

By intravenous injection of euphyllin it was possible to elicit the branch block owing to the increase in frequency, corresponding to the 2 cases reported by Donath (Fig. 4).

Subcutaneous injection of acetyl cholin gave no change in the electrocardiogram of the normal type, whereas this treatment in the presence of the branch block temporarily produced such a marked decrease in the frequency that the block disappeared for a while. On its return we observed the interesting transitional form of 2:1 branch block which is considered extraordinarily rare [Geill (5)] — as shown in Fig. 5.

So, *ceteris paribus*, the presence of branch block is directly dependent on the heart rate, but on daily electrocardiography for some length of time, on some days a low frequency (70) was associated with branch block while on other days a high frequency (115) was associated with an electrocardiogram of the normal type. In a certain period of relatively brief duration electrocardiograms of the normal type were found with the lower pulse rates, whereas the branch block was associated with the higher pulse rate (Fig. 6).

## Discussion.

When two rare affections as myasthenia gravis and intermittent branch block are found in the same patient, we shall naturally be inclined a priori to reckon with a pathophysiological connection between the two morbid conditions. In our case, however, the view of the myasthenia as the cause of the branch block is gain-said by the fact that the block is not abolished or decreased after treatment with prostigmin, which has a favorable effect on the other

symptoms. This, of course, is a serious objection, as hitherto no symptom of myasthenia gravis has failed to improve on treatment with prostigmin, but it is not conclusive. In myasthenia gravis the interstitial accumulation of lymphocytes and degeneration of muscle fibers are often seen in the heart just as in the muscles affected [Ask Upmark (2)], and thus it seems conceivable that the branch block may be due to such a myasthenic muscular degeneration which has interrupted partially the left branch of the conduction bundle, and that this affection has advanced so far that it can no longer be abolished by injection of prostigmin.

The conductivity of the bundle of His-Tawara, moreover, appears to be lowered after treatment with prostigmin, as the block now appeared at a lower pulse rate than before this treatment. Possibly this change may be due to prostigmin although two things go against this: 1) the effect did not appear to commence immediately after the institution of the prostigmin therapy, and 2) intravenous injection of prostigmin was not able to elicit branch block. Perhaps the change is due rather to a varying condition of the myocardium with varying conductivity.

I have not been able in the literature to find any information concerning the effect of prostigmin on intermittent branch block. But in studies on 9 normal persons, Ask Upmark (1) found, among other things, the following features after intravenous injection of prostigmin: prolongation of the conduction time, certain changes in the ST segment and in the T waves, besides, in a few cases, prolongation of the QT interval. Accordingly, in normal subjects, prostigmin has an inhibitory effect on the conduction time and perhaps in the general conductivity of the bundle of His-Tawara.

It would not seem natural to imagine the branch block as a functional result of the myasthenia, as, according to the acetyl cholin theory, we should expect the vagus tonus to be lowered in myasthenia, whereas it is just an increase in the vagus tonus that constitutes the functional cause of branch block.

All told, the various findings seem to indicate that the branch block in our case is not due to the myasthenia. It is more likely that coronary sclerosis forms the organic basis for the block — just as in a majority of the cases reported in the literature.

In our patient, however, there are other cardiac symptoms that are explained best as attributable to the myasthenia gravis.

Thus, in the first electrocardiogram of the normal type we found changes in the ST segments in leads I and II and also in the precordial leads. These changes disappeared definitely under treatment with prostigmin. The T waves, on the other hand, appeared to change independently of the prostigmin therapy, as often they were negative after the branch block had been present for a considerable length of time — something that corresponds to the observations previously reported by Stenström (11). Temporary negativity of the T waves is sometimes seen also after paroxysmal tachycardia and after strumectomy for thyrotoxicosis [Lepeschkin (7)]. Possibly this is a matter of functional changes. Nordenfelt (9) has shown that it is typical of normal subjects to present high T waves with a high vagus tonus, low or even negative T waves with a high tonus of the sympathetic nervous system.

The tachycardia found in our patient on admission was probably due to her myasthenia. Ask Upmark (2) found tachycardia to be constant in his material. In our patient the tachycardia improved under the treatment though not so promptly after the commencement of the continual prostigmin treatment as might be expected of a myasthenic symptom. Possibly there may also have been other factors contributory to the tachycardia — as, for instance, the ephedrin treatment and the slightly increased metabolism.

On the other hand, our patient presented no particularly pronounced dyspnea at rest or on exertion; nor peripheral vascular anomalies. Possibly her shock-like attacks may have been due to the myasthenia, although prostigmin had no effect on the attacks — which may be due to «saturation» of the patient with prostigmin.

### Summary.

Description is given of an instance of intermittent branch block in a patient with myasthenia gravis. Continuous prostigmin therapy and experiments with intravenous injection of prostigmin appear to show that the two lesions are independent of each other. Still, the possibility that the myasthenia may have been the cause of the branch block cannot be excluded conclusively.

The dependency of the branch block on the heart rate is illustrated by tests with euphyllin and acetyl cholin. In this way

the rare phenomenon on intermittent 2:1 branch block is elicited. At the same time, definite myasthenic heart symptoms are demonstrated in the patient.

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*O. A. Bogomoletz*: The influence of the antireticular cytotoxic serum (ACS) upon the healing of bone fractures. (Влияние антиретикулярной цитотоксической сыворотки («Ацс») на заживление переломов). 193 p. Academy of Sciences of the Ukrainian SSR. 1944.

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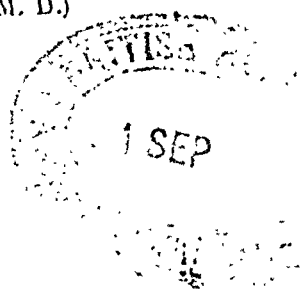
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From the First Medical Department, Sahlgren's Hospital, Gothenburg,  
Sweden. (Acting Head: Dr. Bo Ewert, M. D.)



## Raynaud's Phenomenon in Riveters.

By

TORSTEN LINDQVIST, M.D. and TORSTEN FLEMBERG, M.B.

(Submitted for publication February 22, 1945.)

It has been known for quite a long time that abnormal conditions can arise in the upper extremities in persons working for long periods with tools driven by compressed air. The lesions can occur in the skeleton and the joints, in the form of necrosis in the small bones of the hand or pathologic changes of the deformans type in the joints of the arms and hands; in the vascular system, where circulatory disturbance producing signs and symptoms resembling those of Raynaud's disease may arise; and, in rare cases, in the nervous system. The general opinion seems to be that the damage is caused by the vibrations of the tool, which are transmitted to the hands and arms. Many papers dealing with this complaint have been published. Good reviews are to be found, for instance, in the communications by Feil (1), McLaren (2), Hunt (3), and Jungmanns (4).

In the present paper, we are confining ourselves to a study of the circulatory disturbances arising from operations with tools manipulated by compressed air, special attention having been paid to the question of the anatomic and functional factors at the root of these disorders.

To judge from the literature, the symptoms seem on the whole to be typical. The workmen complain of numbness and cold,

aching and stiffness of the fingers. In addition to this discomfort the skin in the affected areas becomes blanched. The symptoms arise chiefly after exposure to cold, even a slight lowering of the external temperature being sufficient to provoke them. Under the influence of warmth the symptoms soon disappear. In some workmen the symptoms make their appearance only after several years at this type of work, in others after a few months. In general, they seem to be permanent, even though the man in question ceases to operate pneumatic tools.

It is thus an undeniable fact that circulatory disturbance producing on the whole typical symptoms can arise in workmen engaged in operations with tools worked by compressed air. What is the nature of this disorder of the circulation? This question has already been examined, and different views have been expressed on the subject. Hunt (3), who studied seven workmen with this form of occupation, using a satisfactory technique and paying special attention to the dilating capacity of the arteries of the fingers with a raised body temperature, found no signs of structural disease of the arteries in any of his subjects. His investigations proved beyond all doubt that the disturbance can be, and often is, purely spasmodic. However, as his material was small and he does not appear to have selected his subjects from among specially severe cases, it is not impossible that in some cases structural disease might be present in addition to the angiospastic component. Junghanns (4), on the other hand, came to the conclusion that when this syndrome is presented the patient is suffering from endangiitis obliterans, and that an extremely grave condition is therefore in question. He based his view, however, on the examination of a single case, taking the pathologico-anatomic findings from a biopsy specimen to be conclusive evidence. Judging by his description, however, the complaint could quite well have been due to thrombophlebitis migrans without arterial damage. As his material consisted of only one case it is not possible here either to decide whether the symptoms were due to a chance occurrence or whether there actually was an etiologic connection between the work and the illness. Rieder (5), after reviewing 250 persons working with pneumatic tools, was also unable to find a single one with serious signs or symptoms of structural damage. He carried out no special investigations to discover mild degrees of arterial disease, however.

Thiele and Reinhard (6) examined two riveters and seem to have thought it most likely that a spasmodic condition in the vessels was in question. Their investigations were not sufficiently exhaustive, however, to allow definite conclusions to be drawn regarding the nature of the vascular disturbance.

From these remarks it is apparent that the disturbance in the vessels is often purely spasmodic in nature. It can not be said, however, that structural disease can not also be present. More comprehensive studies on a larger material are necessary before this question can be finally decided. The authors of the present paper have therefore attempted to reach a solution of the problem through an investigation on men engaged on this type of work.

*Material.* Our material comprised ten workmen from the Götaverken shipyards in Gothenburg, viz. three riveters and seven riveter's assistants. The work of a riveter consists in riveting iron plates together in the hulls of ships. This is done by means of compressed air, with a tool held by the riveter in both hands while he is working. His assistant stands on the other side of the iron plate and holds in both hands a piece of metal against which the riveter directs his tool. Both the riveter's and his assistant's hands and arms are thus exposed to the vibrations from the riveting tool driven by compressed air. To avoid over-heating, cold air from a tube is played on the tool while the work is in progress. The riveter's hands, especially his right hand, are thus also exposed to quite a considerable degree of cold in addition to the shaking. The assistant's tool is not furnished with any particular cooling apparatus; it becomes hot during the work, and his hands are therefore subjected to a considerable degree of heat.

At the Götaverken shipyards there are about 150 workmen operating pneumatic tools. Our material was especially selected with a view to examining those with the most severe and most persistent symptoms. (The men were chosen after consultation with the health inspector at the yards.) It was presumed that this category would be the most likely to have structural changes. In other respects the men examined were healthy.

The symptoms were similar and typical in all our cases. They consisted in a sensation of cold, stiffness, and numbness, and in blanching of a few, or in some cases of all, the fingers, the paleness covering either the whole finger or only the terminal phalanges. In many instances these symptoms were combined with an aching pain in the fingers. The discomfort had arisen in some cases during the course of the work [cf. Homans, (7)]; when this happened the workmen were forced to rub their fingers or to beat their arms and hands crosswise fashion against their chest before the symptoms would subside. In others, they had appeared also at other times than during work, on exposure to cold, for instance, when the men were bathing out-of-doors during the summer. Cold damp weather seems

to be a dominant provoking factor and in this connection it should be stressed that the temperature by no means needs to be below zero. The discomfort had always subsided under the influence of warmth. Only one out of the ten men examined thought he had noticed that wounds on his fingers did not heal satisfactorily.

The general opinion seems to be that a fairly long period at this type of work must elapse before the circulatory disturbance manifests itself. In our subjects, the symptom-free interval was of varying length, as may be seen from table 1.

Table 1.

Case No.	Work with pneumatic tools No. of years	Symptoms No. of years
1	26	25—26
2	16	10
3	17	16
4	12	6
5	25	10—12
6	7	5
7	15	5—6
8	15	5—6
9	21	19—20
10	20	10

It is not possible to decide whether a spasmodic or an obstructive disturbance in the vessels is in question on the evidence of the subjective symptoms alone. More exhaustive investigations must be carried out before this question can be cleared up.

*Technique.* When choosing our examination method we decided to use measurements of the skin temperature in the fingertips with a rising body temperature [see Gaylor, Uprus and Carmichael (8)], as experience has shown that it is possible with this method to distinguish satisfactorily between spasmodic and structural disorders in the arteries.

The examinations made in this investigation were carried out in the following manner. The subject under examination, clad only in a wollen robe, was made to hold his hands for ten minutes in a pail of water having a temperature of 15° C. By this measure a suitable starting temperature was obtained. He was then asked to remove his hands from the water and dry them thoroughly without rubbing them. The measuring of the skin temperature on the volar surface of the fingertips was then begun. The junctions of the copper-constantan element (a Tykos «Dermatherm») were pressed against each of the fingertips in turn, at such a rate that a recording was obtained once a minute from each of the ten fingers. The values

were read off on the galvanometer. We recorded the temperature for about five minutes. This is sufficiently long to obtain a fully satisfactory idea of the beginning temperature, which remains practically constant for this length of time. The feet and lower legs of the subject were then placed in a bath of water with a temperature of  $44^{\circ}\text{C}$ , and the recording of the temperature in the fingertips was then continued in the same way as before till the arteries were fully dilated. The room temperature was kept around  $15^{\circ}\text{C}$  during the experiments. The temperature in the subject's rectum was taken at the close of the experiment.

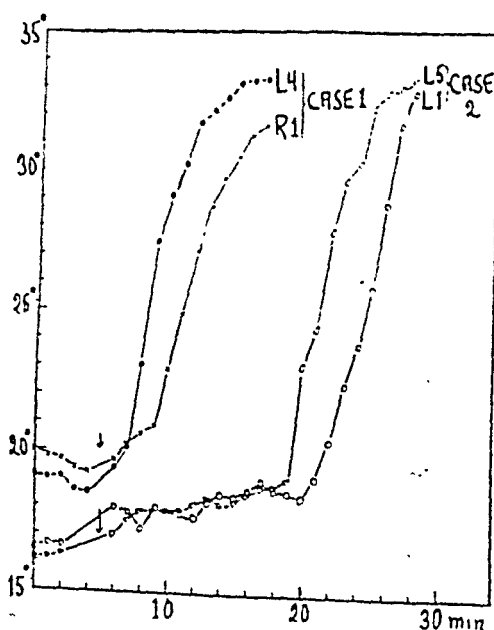


Fig. 1.

*Results.* The ten workmen examined all showed approximately the same features in connection with these temperature tests. Only a few typical cases have therefore been chosen for special mention here. In the curves reproduced, relative to cases 1—3, only the values from two fingers are shown, namely, the finger in which the temperature rise was most rapid and that in which it was slowest. The vertical arrow indicates the moment at which the heating of the body was begun.

*Case 1.* J. E. J., a riveter's assistant, born in 1900. He had been at the work for 26 years. He had had discomfort of the above-mentioned type since he began the work. The symptoms were situated in the four ulnar fingers on both hands, of the same severity in both hands.



As may be seen in figure 1, the temperature in the fingers soon began to rise and increased at a rapid rate. The temperature rise followed a typically normal course, indicating that the arteries were normal. There was nothing to indicate either spasm or structural disease.

*Case 2.* E. E. A., a riveter, born in 1909. He had been doing this type of work for 16 years. He had had the typical symptoms for the past 10 years, all his fingers being affected, to an equal degree in both hands.

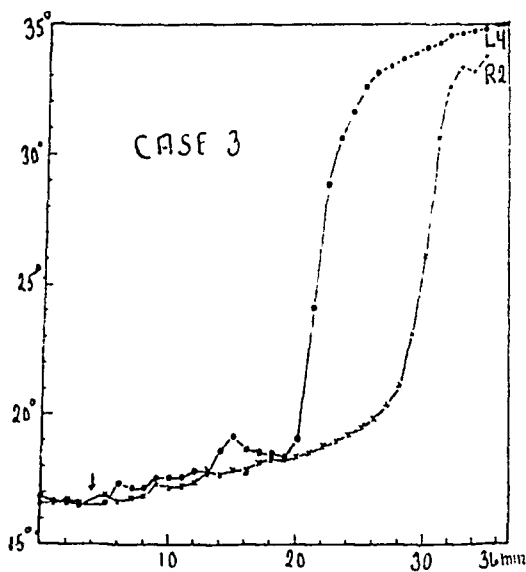


Fig. 2.

In this case the dilatation (see fig. 1) occurred later, but when once the rise had started it proceeded rapidly, as it had done in the first case. Here, in all probability, there was a spasmodic obstruction, but it soon relaxed. As in the first case, so here also there was no reason to suspect the presence of structural changes in the arteries.

*Case 3.* E. G. N., a riveter's assistant, born in 1903. He had been engaged on work with pneumatic tools for 17 years, and had been suffering from the typical symptoms in all his fingers for 16 years, no difference being noted between the right and the left hands.

Figure 2 shows that, as in case 2, the temperature rise occurred fairly late, up to 20 minutes after the heating was begun. Here, a spasmodic obstruction was undoubtedly present. When once the temperature rise had started, however, it proceeded rapidly and the presence of structural changes in the arteries thus seemed unlikely.

Case 4. V. E. O., a riveter's assistant, born in 1908. He had been 12 years at the work, and had had the typical symptoms for about 6 years. The four ulnar fingers on both hands were affected, to the same degree in both hands.

The four fingers for which the results are illustrated behaved somewhat differently (see fig. 3). The little finger on the right hand yielded a completely normal curve, with an early and rapid rise in the temperature. In the left thumb the dilatation started later but then proceeded rapidly.

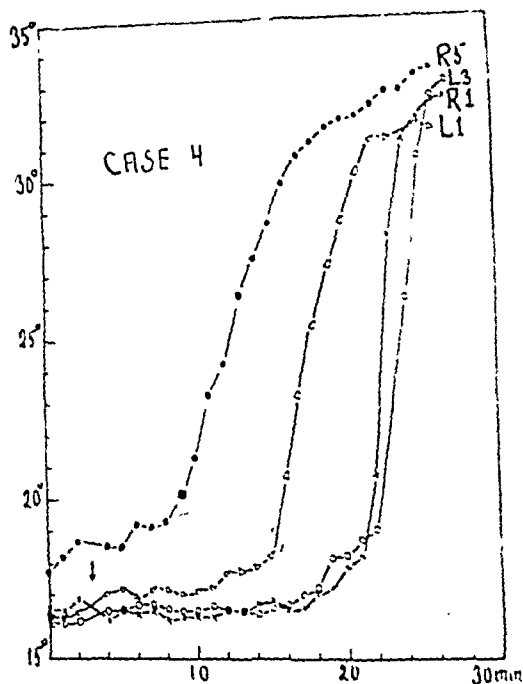


Fig. 3.

In the right thumb and the left middle finger the dilatation was even more delayed. After it had started, however, there was a very quick rise. Vascular spasm was obviously present in both these fingers. In this man also, there were no signs to indicate structural changes. During the course of the experiment a few clinical observations of interest were made in this case. After exposure to cold the four ulnar fingers on the left hand were noticeably blanched, and this phenomenon lasted for about fifteen minutes after the heating of the body was begun. The paleness was then replaced by redness. Similar blanching was observed in the second and third fingers on the right hand. This feature did not become apparent, however, until about ten minutes after the heating was begun. There seems to have been no definite connection between these features and the course of the dilatation. Thus, the right thumb, in which the dilatation was delayed, displayed no change in colour. Of the four ulnar fingers on the right hand,

the rise in the temperature occurred later in the second and third fingers, however, a fact which was to be expected in view of the clinical signs. In the fingers on the left hand the signs and symptoms and the course of the temperature curve were in better agreement; the arteries in the thumb, which showed no clinical signs, dilated first, the other fingers later, and among these the third finger lagged behind noticeably.

Approximately the same picture was present in the other six men. In no case were there any signs of structural damage.

In addition to these ten cases we are appending a further case which was not included originally in the investigation but which is worth mentioning because it contained features of particular interest in the present connection.

*Case 11.* A. O., a riveter, born in 1904. [Previously described by Lindqvist, (9).] He had been doing this type of work for the past few years and had had the same symptoms, blanching and numbness of the fingers, as the others. On May 20, 1943, he hurt his right hand in a bicycle accident, sustaining a wound on the back of the hand, at the base of the third and fourth fingers. This wound was stitched, but began to suppurate after a few days. It gradually healed, however. As he had also sustained a rupture of the extensor tendon of the right little finger at its insertion into the terminal phalanx he could not return to work. The rupture did not heal spontaneously and his finger was therefore put in plaster on June 15. When examined on June 26 he complained of an ache and a sensation of cold in the third and fourth fingers on the right hand, and his fingers were found to be cyanotic and cold. He was given priscol, but no improvement was noted. At an examination on July 8 he reported that after another slight accident a blister had appeared on the terminal phalanx of the third finger. The blister was cut away and the wound healed by third intention but around July 20 a couple of small blood blisters appeared spontaneously immediately above the site of the first blister. The wound made by these blisters was slow in healing. As arterial damage was suspected the patient was examined by the method described earlier in this paper. The result is shown in figure 4.

The fingers on the left hand all yielded practically the same value as the middle finger. The little finger on the right hand behaved similarly to the ring finger. The examination proved that the temperature in the middle finger on the right hand rose at a much slower rate than that in the other fingers. It seemed obvious that arterial obstruction was present in this finger. The same features were present in the right index finger but the obstruction was less severe in this finger. In the other fingers on the right hand the temperature rise was slightly slower than in the left hand, but from a diagnostic point of view no definite significance can be placed on this observation. From the measurements taken at the base of the middle fingers it was also established that in the right hand the elevation in tem-

perature took place sooner at the base than at the tip of the fingers, while in the left hand the rise at the tip was in advance of that at the base. This is also a sign that there was arterial obstruction in the right hand.

Can we consider this obstruction to be a result of the trauma, or was it present before the injury and due to the patient's occupation? Judging by the findings from the other men, in none of whom arterial damage could be demonstrated despite the presence of severe symptoms, it seems improbable that in this patient the narrowing of the vascular lumen could

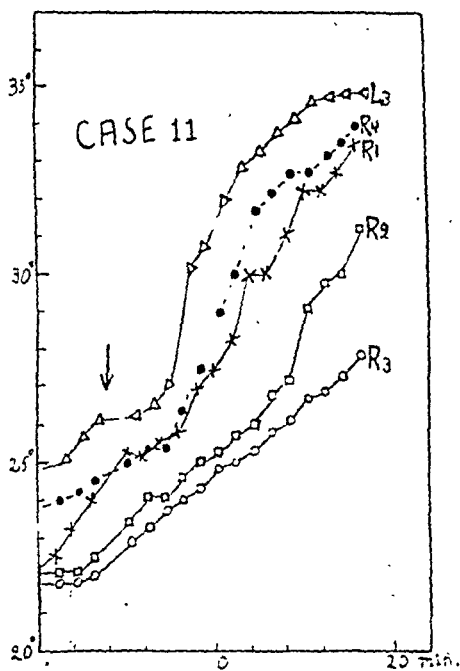


Fig. 4.

have arisen in consequence of his work. The most likely explanation, therefore, is that a thrombotic process arose in the arteries of the second and third fingers of the right hand following the trauma or the secondary infection. Owing to the nature of the complaint he was advised to give up all work with tools driven by compressed air.

In five of the men we attempted to influence the symptoms with priscol. When they used this preparation, in a dose of 0.025 g, they all stated that the symptoms were less severe or entirely absent when their hands were exposed to cold when away from work, but that while the work was in progress they could observe no change in the symptoms.

Thus, in none of the men examined were there any grounds for assuming that their occupation had given rise to structural changes

in the arteries. In some of them arterial spasm was present, in others the vessels reacted absolutely normally during the tests. Our material is admittedly rather small, but as it includes only those who had discomfort of long standing and of great severity from among a very large number of workmen with symptoms it cannot be denied that its value as a means of demonstrating the absence of this type of structural disease is fairly high. There seem, in fact, to be no established cases of structural disease of the arteries having this genesis. The case described by Junghanns, as we pointed out earlier, can not be attributed any value as evidence to the contrary.

We therefore consider the circulatory disturbance occurring in workmen operating pneumatic tools to be of a functional nature.

### Summary.

Although there already exist a large number of publications on circulatory disturbances arising as the result of operations with pneumatic tools, the nature of these disturbances has remained unclear. Some observers consider that structural changes in the arteries are present in these cases, others that arterial spasm forms the genetic factor. The authors of the present paper have examined ten men, those with the severest symptoms in a group of 150 workmen. The examinations were carried out by the method of measuring the skin temperature in the fingers with simultaneous raising of the body temperature. In none of the men was it possible to demonstrate structural disease. In some there was severe, in others moderate vascular spasm, and in the rest the reactions of the vessels were quite normal. We believe, therefore, that the circulatory disturbances in workmen operating tools driven by compressed air are of a functional nature and not due to structural change.

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From the Medical Clinic A of the University of Copenhagen, the Righospital, (Chief: Professor Carl Sonne, M.D.) and from the Medical Department of the Militærhospital, Copenhagen (Chief: Chr. N. J. Gram, M.D.).

## Studies on the effort syndrome.

### II. The Conditions of the Large Arteries During Muscular Work Illustrated by Oscillometric Measurements.<sup>1</sup>

By

B. CHR. CHRISTENSEN, M. D.

(Submitted for publication June 6, 1944.)

In a previous work by the author (1944, c) it has been demonstrated that patients suffering from the effort syndrome are able to carry out rather great bodily work, and that the variations in the arterial pressures and the pulse rate during muscular work are the same as are seen in normal persons of the same sex and age.

In the article here presented an account will be given of the oscillometrically demonstrable changes in the conditions of the large arteries during muscular work.

Bergman (1922) has made oscillometric measurements during muscular work but has found no changes in the range of the maximal oscillation nor in the shape of the oscillometric curve.

Eldahl (1933) and Em. Hansen (1937) have likewise made oscillometric measurements during muscular work by means of an optically registering oscillograph constructed by Eldahl. These writers did not either, even at hard muscular work, succeed in demonstrating a change in the shape of the oscillometric curve, which is probably due to the fact that the oscillograph applied by them was not sufficiently sensitive.

<sup>1</sup> The investigations have been carried out with financial support from the Kong Christian den Tiende's Fund and from Miss P. A. Brandt's Scholarship.

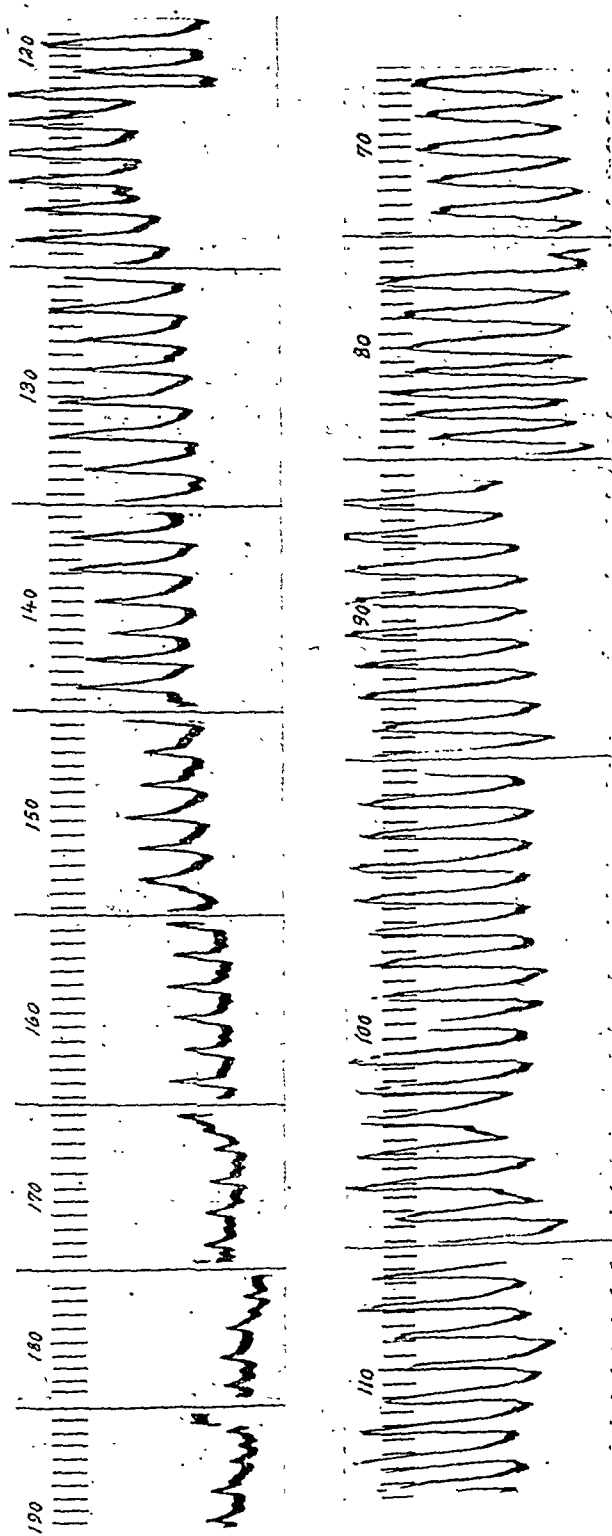


Fig. 1. Oscillographic film registered during the carrying out of 900 kilogrammeter (kgm) per minute. The figures above the curve indicate the pressures in the compressing cuff.

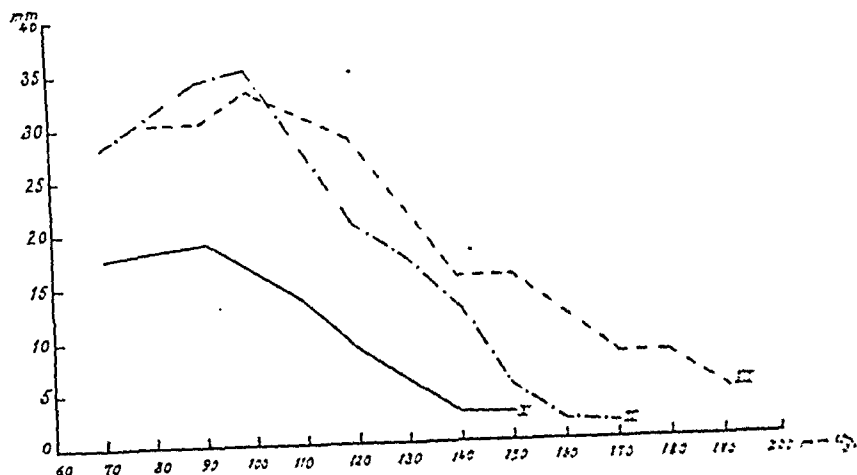


Fig. 2. 3 oscillometric curves from experiment No. 75. Curve I registered immediately before the commencement of the work, curve II just after the start of the work, and curve III after 20 minutes of work.

### *Own Investigations.*

For these investigations an optically registering oscillograph was applied, a description of which has been given in a previous work (1944, a).

On Krogh's bicycleergometer working experiments were made with 8 normal young men and 8 young male patients suffering from the effort syndrome. Both the normals and the patients carried out work of from 300 to 1200 kgm per minute for up to 30 minutes. In this article mention will be made of the oscillographic curves registered immediately before the commencement of the work, just after its start, and just before its discontinuation.

### *Normal Persons.*

Fig. 1 serves as an example of an oscillographic film produced during the carrying out of a work of 900 kgm per minute. The oscillometric curve calculated from this film presents no peculiarities, so accordingly there is no need to describe it further here.

Fig. 2 is from experiment No. 75, in which the person experimented on, No. 2, carried out 1200 kgm per minute for 30 minutes, an amount of work that did not tire the person in question. It is seen that curves II and III are alike in size and of the same shape as curve I, which must signify that the arterial wall has the



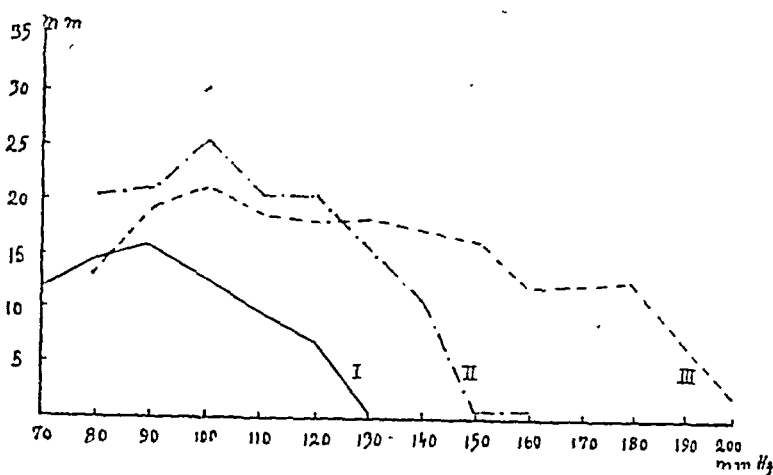


Fig. 3. 3 oscillometric curves from experiment No. 76. Curve I registered immediately before the commencement of the work, curve II just after the start of the work, and curve III after 29 minutes of work.

same pressure-volume curve as when the muscles are at rest. The increased maximal oscillation in proportion to the resting curve is caused by the increased arterial pressures with a resulting greater arterial diameter. 7 of the normal persons showed in all working experiments the same conditions.

Fig. 3 is from experiment No. 76 in which the 8<sup>th</sup> person experimented on, carried out a work of 1200 kgm per minute for 30 minutes. In this case curve III is seen to have become changed, being somewhat flattened and lower than curve II. This change is indicative of some contraction of the arterial wall. A similar curve has been obtained at another working experiment, likewise with a work of 1200 kgm per minute, whereas no such change in the shape of the curve has been observed at the carrying out of a work of 900 kgm per minute for 30 minutes. This means that in this normal person there occur oscillometric curves that are indicative of a constriction of the branchial artery, whenever the person carries out great bodily works.

It would be tempting to make oscillometric measurements at still greater amounts of work in order to make out whether it were possible in all normals to demonstrate arterial contraction during muscular work. However, such experiments cannot be undertaken with the technique applied at these investigations, because it is impossible for a person experimented on to keep one arm

quiet and relaxed and at the same time carry out works exceeding 1200 kgm per minute.

It would also be interesting to see whether there occurred similar contractions in the large arteries of the working extremities. This cannot, however, be explained by means of the oscillometric method, the latter being only applicable to extremities at rest with relaxed muscles. As the oscillometric curve alters its shape towards the normal at the discontinuation of the work there is no possibility either of demonstrating this change in the curve by oscillometric investigations of the working extremity immediately on the discontinuation of the work.

### *Patients Suffering from the Effort Syndrome.*

As mentioned in the preceding there appeared in a few cases in normals a change in the shape of the oscillometric curve during muscular work, a change that was indicative of a contraction of the wall of the artery measured on. As suggested in an earlier work (1944, c) there occurs frequently in patients with the effort syndrome a fall in the maximal oscillation during muscular work; and it has been pointed out that this fall occurs also at works requiring but little effort of the persons concerned.

2 examples are given here of oscillometric curves registered while patients with the effort syndrome were doing muscular work. Figs. 4 and 5 are from experiment No. 135 in which there was performed a work of 900 kgm per minute for 30 minutes. Fig. 4, which was produced just after the commencement of the work, illustrates the normal variations of the oscillations at the different cuff pressures. Fig. 5, produced after 29 minutes of work, shows plainly that the oscillations have become small and almost equal in height over a rather large pressure area.

For each of the experiments 3 oscillometric curves have been registered in the manner mentioned in the preceding, i.e. one curve immediately before the commencement of the work (curve I), one just after the start of the work (curve II), and finally one just before the discontinuation of the work (curve III).

Fig. 6, from an experiment in which patient No. 6 carried out 300 kgm per minute for 30 minutes, serves as an example of a typical change of the oscillometric curve at even very light work.

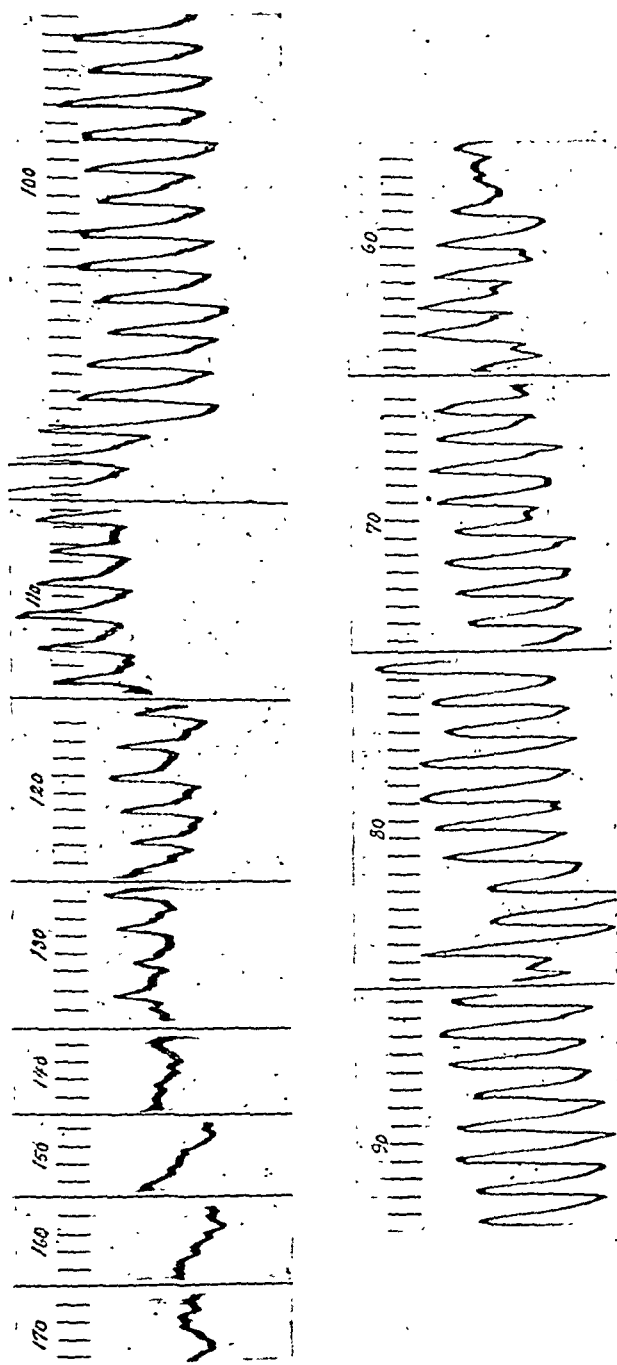


Fig. 4. Oscillometric film from experiment No. 135 registered immediately after the beginning of the work. The figures above the curve indicate the pressures in the compressing cuff.

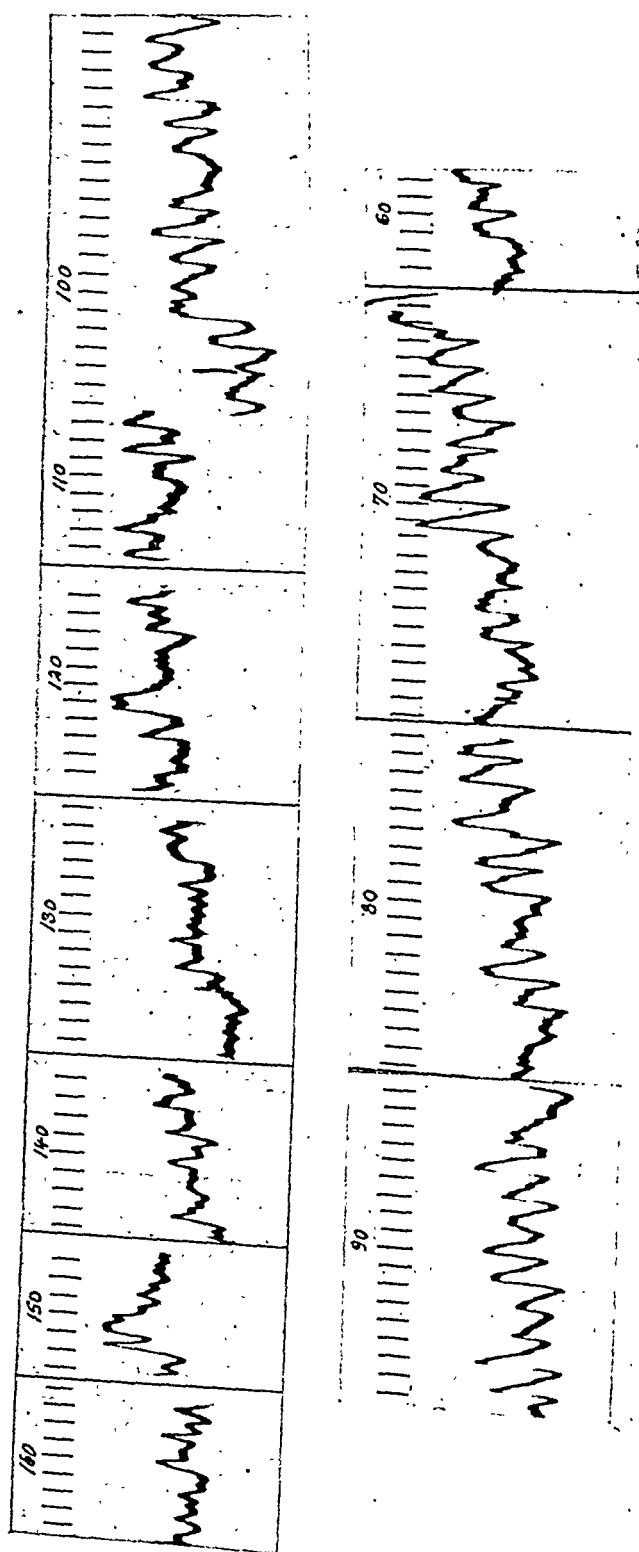


Fig. 5. Oscillometric film from experiment No. 135 registered after 29 minutes of work. The figures above the curve indicate the pressures in the compressing cuff.

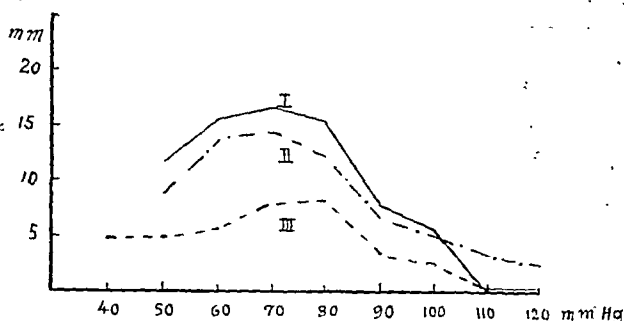


Fig. 6. 3 oscillometric curves from experiment No. 129. Curve I registered immediately before the commencement of the work, curve II just after the start of the work, and curve III after 29 minutes of work.

It appears plainly that curve II, registered immediately on the start of the work, is lower and more flattened than the curve registered at rest, and that curve III, registered after 29 minutes of work, has the shape found when the artery measured on is contracted.

In experiment No. 97 patient No. 5 performed a work of 600 kgm per minute for 30 minutes without any troubles for the patient. Fig. 7 shows that curve III, registered after 29 minutes of work, has become flattened and plateau-shaped as a sign that the artery measured on is contracted. All the other patients showed at the same work a similar alteration of the oscillometric curve registered after 29 minutes of work.

Experiment No. 85, carried out by patient No. 3, shows the variations during a work of 1200 kgm per minute for 11 minutes, which was this patient's maximal capacity. Fig. 8 renders the 3 oscillometric curves. Curve III, registered immediately before the discontinuation of the work, is here seen to be pronouncedly deformed, the range of the oscillations being practically the same at pressures from without varying from 190 to 80 mm.

From the examples instanced here of working experiments with relatively small amounts of work it appears that during muscular work there occurs a marked change of the oscillometric curve in patients suffering from the effort syndrome. Further it appears that this change occurs already at work which the patients in question can carry out without feeling tired, and finally that it gets more and more pronounced at increasing amounts of work.

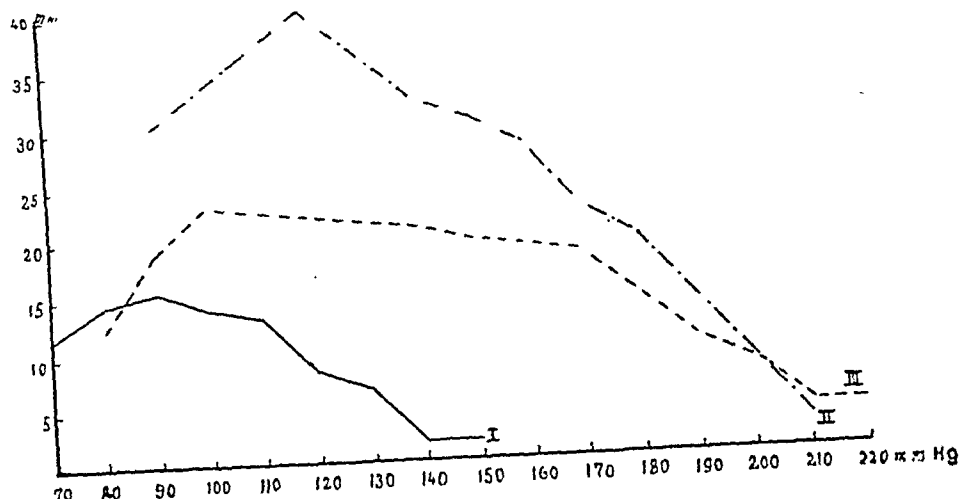


Fig. 7. 3 oscillometric curves from experiment No. 97. Curve I registered immediately before the commencement of the work, curve II just after the start of the work, and curve III after 29 minutes of work.

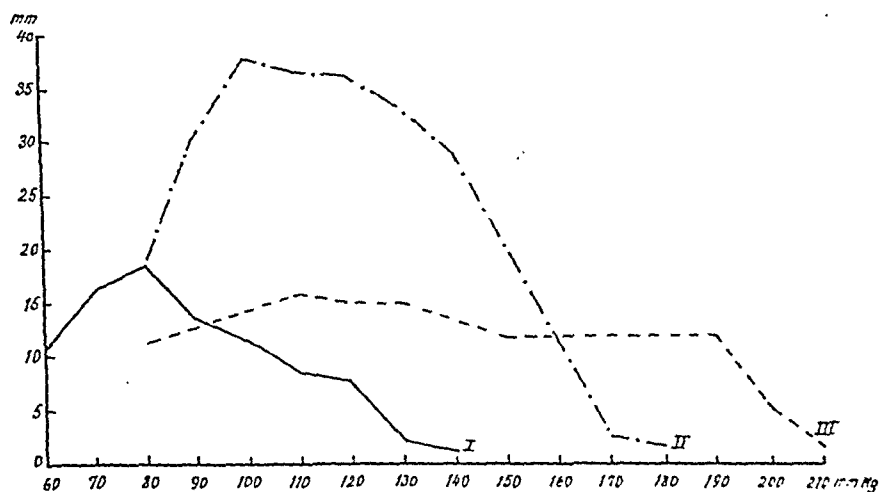


Fig. 8. 3 oscillometric curves from experiment No. 85. Curve I registered immediately before the commencement of the work, curve II just after the start of the work, and curve III after 29 minutes of work.

This change in the shape of the oscillometric curve shows that in patients with the effort syndrome there occurs constriction of the large arteries during work, and that this constriction is often seen to appear at work that the patient is able to perform without getting tired. As mentioned before, these changes are only demonstrable in the arteries outside the working areas.

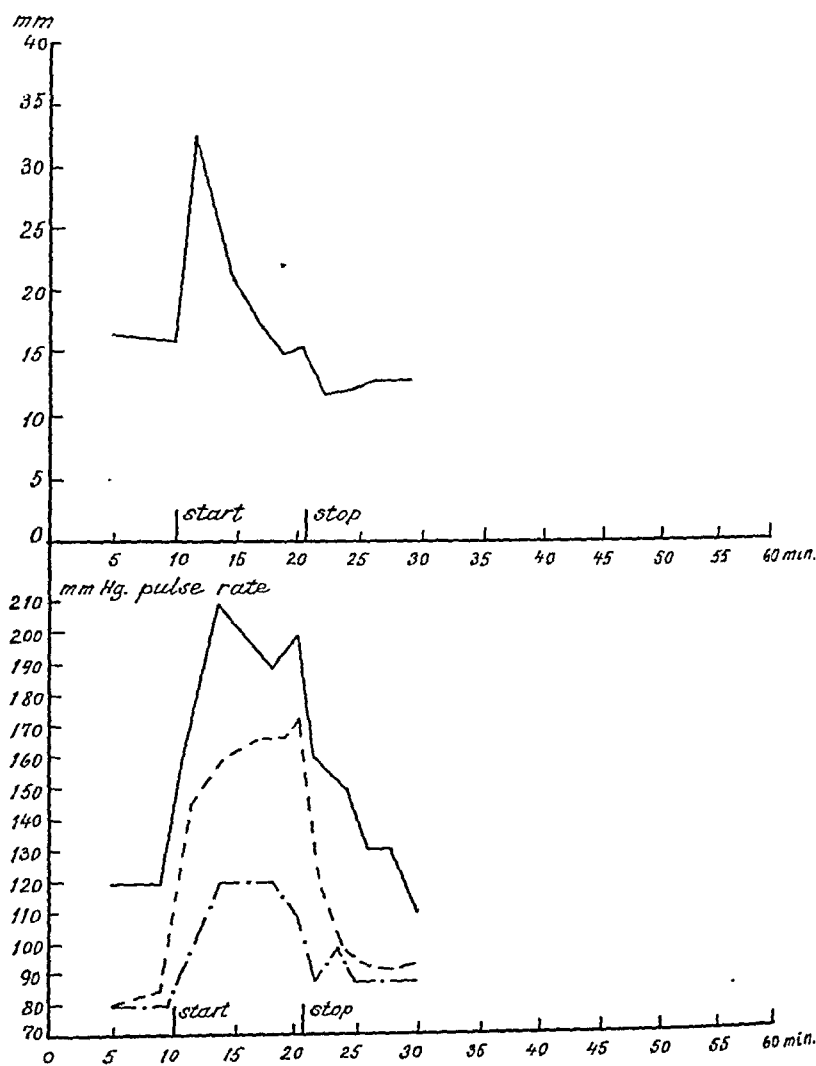


Fig. 9. The variations in the arterial pressures, the pulse frequency, and the range of the maximal oscillation in experiment No. 85. Uninterrupted line indicates the 1st pressure, — — — the 2nd pressure, and — · — the pulse frequency. The abscissa indicates the time in minutes. The ordinate: Lower section = the values of the arterial pressures and the pulse frequency. Upper section = the variations in the range of the maximal oscillation expressed in mm.

The change mentioned here in the state of the arterial wall affects highly the palpatory estimation of the pulse. Thus at many of the experiments it was hardly possible to count the pulse by palpation of the radial artery. The pulse was «all but impalpable».

A comparison of the observations mentioned here with the

conditions seen in the normal persons shows the essential difference between the two groups to be this that in the patients the arterial constriction occurs at works which they are able to carry out without feeling tired, and that the changes are constant in the patients.

The most obvious explanation of the constrictions demonstrated here in the large arteries outside the working muscle areas is that they should form part of a collateral vasoconstriction to lighten the venous return and with it the increased requirement of the minute volume of the heart, a theory advanced by the author in 1941.

In case now the large arteries should take part in the general circulatory regulation we should quite naturally imagine a similar constriction to be demonstrable at other requirements on the blood circulation.

The author has therefore made oscillometric measurements on 2 normal young men and 2 young male patients with the effort syndrome during change of posture on a tilting table. The conditions were investigated with the person in question taking up the passively standing position, i. e. with relaxed lower extremities, a position that makes great requirements on the circulation (Hohwü Christensen & collaborators). Numerous experiments were made with measurings on both the brachium and the femur, but not in a single case any change in the oscillometric curve was observed, not even in the cases in which there occurred a fall in the blood pressure during the experiment.

To be true the arterial constriction demonstrated during muscular work does not have the character of a response to nervous reflexes, as it does not occur momentarily but gradually during the work. Thus fig. 9 shows that the maximal oscillation rises steeply at first together with the rise in the blood pressure, then to fall slowly while at the same time the blood pressure remains rather unchanged.

As mentioned in a previous work by the author (1944, c), Sonne (1923) has advanced the hypothesis that the symptoms of effort syndrome should be simple acapnial symptoms caused by hyperventilation during muscular work, and that Soley & Shock (1938) and Guttman & Jones (1940) have managed to provoke the typical symptoms on the patients by hyperventilation at rest.



In another work (1944, b) the author mentions the demonstration of the fact that any form of ventilation causing release of carbon dioxide brings about in normals a constriction of the large arteries at a time when subjective symptoms of acapnia have not yet occurred.

Accordingly the presumption suggests itself that the constrictions of the large arteries demonstrable during muscular work are due to the fact that the individuals in question hyperventilate during work thereby releasing  $\text{CO}_2$ .

This fact has been investigated further by means of experiments in which the persons checked their respiration voluntarily during the work. Be it said at once that such experiments are very difficult for the persons to carry through. First it is even for a normal person difficult to check the respiration voluntarily during relatively hard muscular work, and secondly he must, coincidently with his checking of the respiration, take care that the arm measured on is kept completely relaxed and at muscular rest. Finally he must during the whole work ride in time to a metronome.

The principle of these experiments was to let the patient work until, by observations of the oscillations of the optic index in the oscillograph, the experiment conductor suspected that the oscillometric curve had changed its shape. When this had happened the patient was ordered to check his respiration as much as he could, and at the same time it was tried to register one or more oscillometric curves. When he could not check his respiration any longer he made a sign to the experiment conductor.

After many training experiments had been made, 5 such experiments were finally carried through on 3 patients.

It appears that the arterial pressures and the pulse rate are uninfluenced by the checked respiration and that the maximal oscillation increases considerably as long as the respiration is checked.

A view of the individual oscillometric curves shows that during the checked respiration the curve changes its shape getting to resemble the normal oscillometric curve.

Fig. 10 illustrates this fact. Curve I was registered before the patient checked his respiration, curve II during the checking, and curve III when he breathed «normally» again. It is seen plainly that curve II is of an almost normal shape.

Thus these experiments show that the arterial constriction

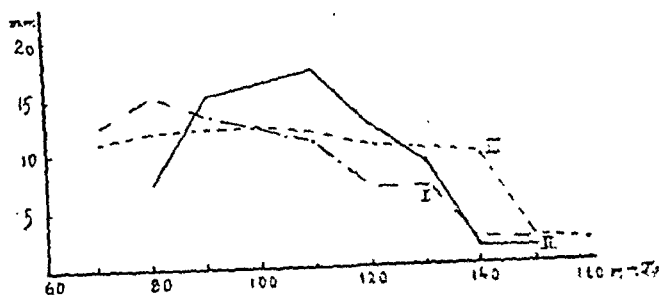


Fig. 10. 3 oscillometric curves from experiment No. 131. Curve I registered before the person checked his respiration, curve II during the checking, and curve III after the checked respiration.

occurring during work in patients suffering from the effort syndrome can be removed when the patients in question check their respiration. On the basis of the previously mentioned work by the author (1944, b) there is reason to presume that it is the carbon dioxide tension increased during the checked respiration that removes the arterial constriction.

### Summary.

A description is given of the author's oscillometric investigations of normals and patients with the effort syndrome while they were doing muscular work. It appears from these investigations that normals may occasionally during work present oscillometric curves that must be caused by contraction of the wall of the artery measured on. These changes are not constant being only observable at fatiguing works. But in the patients a constant arterial constriction is demonstrable even at the works that are easy for them to perform (600 kgm per minute). At fatiguing works this change becomes more pronounced. This fact is elucidated by various examples. Thus it appears from this series of investigations that there is a difference on this point between the normals and the patients with regard to their response to work.

Then the cause of the arterial constriction is discussed, and the author arrives at the result that the constriction may be due to hyperventilation with a resulting reduced  $\text{CO}_2$ -tension in the arterial blood. For a further investigation of this fact oscillometric examinations have been made during muscular work with checked respiration. These examinations show that the oscillometrically

demonstrable constriction of the large arteries can be removed when the person experimented on checks his respiration voluntarily during the muscular work. This observation collated with previous investigations made by the author are indicative that the patients suffering from the effort syndrome hyperventilate during muscular work, a fact that bears out Sonne's hypothesis that the symptoms of the effort syndrome are acapnial symptoms.

Finally it should be mentioned that at the investigations mentioned here there has been demonstrated no qualitative difference between the response to work of the patients and that of the normals. This favours Lewis' hypothesis that the symptoms in the patients are ordinary phenomena of fatigue, and that the only difference between the normals and the patients is that the latter get tired more quickly than the former. Accordingly the author is of opinion that Lewis' term »effort syndrome» should be the term applied.

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From the Neurological Department of the Aarhus City Hospital, Aarhus,  
Denmark (Chief: Professor C. J. Munch-Petersen, M. D.).

## Rothmund-Werner's disease.<sup>1</sup>

A Case with Internal Frontal Hyperostosis.

By

ASGER LOUW.

(Submitted for publication February 28, 1945).

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A good many diseases are known merely as an aggregate of symptoms — syndromes — the true connection of which is still obscure. Often they are represented by the »rare cases» which appear to be of no great significance in the daily practice of medicine, and yet they are of some importance, being not merely curiosities. As »multifaceted stone(s), difficult to place, but, once adapted, capable of illuminating the entirety». They may turn out to be the way leading to the depth of some pathological problems.

While working with the clinical aspects of the frontal hyperostosis I have met with a patient who presented an uncommon nosographic picture of that kind. As far as I have been able to find out, the Scandinavian literature has not yet brought any other report on a similar case. It will be appropriate, therefore, first to give a detailed account of the case history and symptoms of this patient and then what little is known about the disease.

### *Case History.*

The patient is a woman, 43 years old, who has been granted invalidity benefit. On 21/3/1944 she was admitted to the Neurological Department of the Aarhus City Hospital for observation.

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<sup>1</sup> Read before the Association of Younger Hospital Physicians in Aarhus on April 25, 1944.

She is No. 6 of 7 siblings. 1 brother died of tuberculosis, but all the other sibs were said to be well. The parents died at an early age; the father died of pulmonary tuberculosis at the age of 40. In previous certificates to the Invalidity Insurance Council it says that he was alcoholic, but this characterization is denied by the sisters of the patient who claim that he consumed alcohol only in a light degree like so many others at that time.

The mother committed suicide at the age of 44, during an attack of melancholy.

Otherwise the family history is claimed to be negative as to diseases or manifestations of morbid character, and — what is important in this connection — the case of our patient is unique in the family.

Up to the age of 5 years her development is said to have been normal in every respect. Her parents died when she was 5 years old, and she was placed in a children's home, where she stayed till she was 27 years old.

She had always been thin and delicate of build, though able to run about and play like other children. Now her development became quite abnormal, however. Her growth was retarded and she became horribly emaciated. The muscles of her arms and legs wasted away or failed to develop; and the muscular power was very low. She was examined several times with a view to the possibility of tuberculosis, but no evidence of a tuberculous infection could be found.

Concerning her childhood she says herself in a secretive whisper: »It was my nerves that got bad because I never was allowed to get out; I always had to stay indoors.» She quit taking food because she thought she would die anyhow. She could hardly swallow and had no spittle in her mouth. She further said that when she was on a picnic with the other children of the home she ran away from them in order to hide her appearance, and she would pinch her arm to see if she really was alive.

After her confirmation she tried some situations as nursemaid and as milliner's apprentice, but she could not keep any of them. She was clumsy, her hands and feet shook and she was not strong enough to lift a bucket of water. She returned to the children's home where she was given an easy occupation — sewing, mending, and playing with the children.

Her sexual maturity appears to have proceeded normally. The menstruation commenced at the age of 13 and continued regularly, though always most scantily, till the appearance of the menopause at the age of 39.

Also her mental habitus appears not to have suffered any particular impairment during her illness; it has merely preserved a distinct infantile character. She attended school till her 15th year and got along well, although she was always very nervous and sensitive to the noise of the other children.

At the age of 27 she was granted invalidity benefit because of her defective development, her dwarfish growth and neurasthenia. At that time she measured 148 cm in height and weighed 29.5 kg. A single determination of the metabolism showed a rate of 88 %.

At this time the skin of her feet began to undergo some marked changes. Her skin had always been dry and scaly, but within a few years there

now developed a marked degree of sclerodermia on the feet and legs; later, also the skin of her hands and face became sclerodermic but in a lesser degree.

Both in childhood and later the patient had trouble in walking because there was no flesh on her feet. In 1929 she was given orthopedic treatment for pedes plano valgi fixati with flat-foot boots, which were renewed in 1934. Gradually, however, it became impossible for her to walk because of the appearance of ulcerations and inflammatory processes on her feet that would not heal. For the past 4—5 years these suppurative refractory ulcerations have forced her to keep to her bed, partly at home, partly in the Sæby Hospital, where a sequestrum was removed from one of the ulcers.

At the age of 35—36 years, impairment of the vision commenced insidiously, leading to operation for cataract of the right eye in 1938. At that time the visual acuity of the left eye was fairly good, but it has decreased markedly since, and now the patient is able merely to make out lamplight, strong colors and the rough outline of persons.

From her 9th to her 40th year the patient has had long periods of intense and persistent headache, referred to the occipital and parietal region as a pressing band, without the character of migraine. She has been troubled a great deal with poor sleep and constantly with overwhelming tiredness.

In June 1935, after several convulsive attacks, the patient was admitted to the Sæby Hospital in a comatous state; no particular information about this condition could be obtained. In November 1938 she was admitted to the Hjørring County and City Hospital for the sake of a thorough examination on account of an application for an increase in her invalidity benefit. On this occasion it was discovered that the patient is suffering from diabetes: + glycosuria (Lohnstein 0.3); + diacetic acid; — acetone. Blood sugar: 228—180 mg %.

Glucose tolerance test: maximal rise to 370 mg % after 1 hour; 265 mg % after 4 hours.

In addition, *hyperostosis of the cranium* was revealed.

Roentgenography of the skull showed: Form natural. Most of the walls very thick; in the frontal region unquestionable pathological thickness, measuring up to 2 cm. Here the walls are completely sclerotic and the posterior border is very irregular. The arterial configuration is very distinct on both sides, with the same caliber. The impressions are not accentuated. Sella turcica normal.

Further, *atrophy of bones and halisteresis* are demonstrated roentgenographically.

X-ray examination of the left foot: The skeleton is markedly underdeveloped and the calcium content of the bone is low. X-ray exam. of the lower half of the left leg: Scattered areas of rarefaction in the tibia, particularly pronounced about 6 cm. above the ankle, without density of the surroundings. The corresponding part of the fibula shows rather sharply defined atrophy of the bone here and there.



Fig. 1.

(All descriptions signed Rask-Nielsen.)

Laboratory examinations reveal a state of *hypocalcemia*: Serum calcium, 8.7—8.4 mg %. Otherwise no abnormality: Metabolism, 108—97 %. specific gravity of the urine, 1020—1036. Hormonal analysis: 12.5 R. U. gonadotropic hormone per 24 hours.

At that time her condition was designated as an insufficiency-dysfunction of one or more internal secretory glands, including the pituitary and possibly the thymus.

In the past year the patient has stayed in the Sæby Hospital. Here the blood sugar concentration was about 300 mg %, and the patient was given ordinary diet minus sugar, and she was treated with insulin retard, 12 + 6 units daily.

As the ulcerations on her feet would not heal, the advisability of an amputation was considered. Before this, however, a thorough examination seemed desirable with a view to the peculiar atrophy of the bones and muscles in this patient.

*Physical Examination.* — The peculiar appearance of the patient is conspicuous at the first glance (Fig. 1).

Although the skull is normal in form, the facial part seems small and poorly developed — owing to atrophy of the soft parts. The mouth is thin, the lips are taut, the nose sharp and pointed. The physiomy is dominated by a pair of lively eyes. The eye slit is large and the bulb protruding,

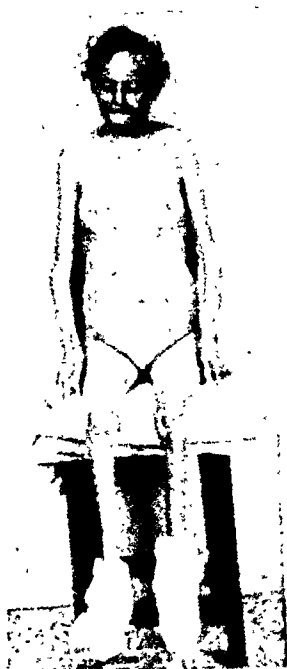


Fig. 2.

but undoubtedly this is merely a pseudo-exophthalmus owing to atrophy of bones and soft parts. Thus the face has the characteristic stamp, reminding of a bird of prey.

The patient measures 148 cm in height and weighs only 30.9 kg. Thus her nutrition is far below medium, but there is no diffuse emaciation. The trunk is fairly voluminous with a normal panniculus adiposus. The breasts are small, undeveloped, without any palpable glandular tissue. The trunk on the whole is of infantile proportions. The abdomen is somewhat protruding. In sharp contrast hereto, the arms and legs are thin, skeleton-like (Figs. 2 and 3).

The hair is thin and tousled, almost grey. The hirci and pubes are normal. Supercilia scanty. The voice is crisp, but not hoarse.

Her mental habitus is infantile but not really inferior. Her memory appears well-preserved, and she is willing to give a detailed account of her illness. Her behavior in the hospital is excellent.

Subsequently the following features were noted in her record:

Iridectomy has been performed for cataract of the right eye; there is a mature cataract of the left eye.

The cranial nerves are intact. No enlargement of the thyroid.

Throat normal. Auscultation of the heart and lungs normal.

Abdomen rather voluminous, otherwise normal.

The extremities are characterized by the extreme muscular atrophy,



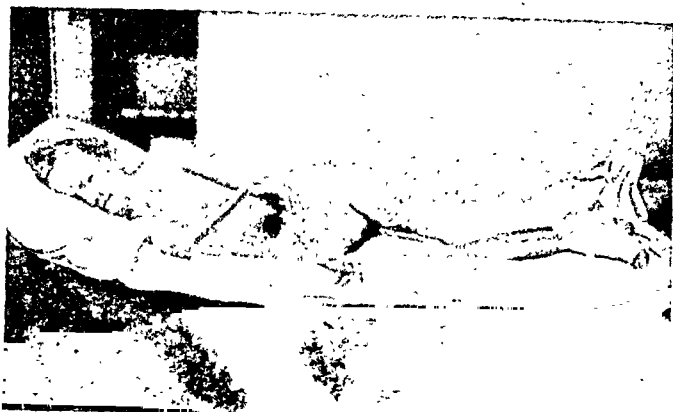


Fig. 3.

the very thin bones and — for the lower extremities — complete transformation of the skin.

It looks as if the skin had been pulled directly over the skeleton; the strength of all the muscle groups is very low. The hands with their thin gracile bones, the protruding tendons and the dry, scaling, atrophic skin look and feel like the claws of a bird. There is free mobility in all the joints of the upper extremities, no sensory disturbances, and the deep reflexes are present.

On the lower extremities the changes are really to be characterized as monstrous. The feet are quite deformed as a result of the advanced atrophy of all the tissues (Fig. 4). They are pointed and shrunken from the ankle to the toes as if from childhood they had been laced forcibly with tight bands. From the first to the fifth toe, the toes are increasingly dwarfed, so that the fifth almost looks merely like a wart. Distally from the middle of the legs the entire skin is the site of a very pronounced scleroderma, and this process is farthest advanced on the feet. Here the skin has completely lost its original character, becoming stiff, cracked and firmly attached to the underlying structures. The peculiar glistening, pink, surface with scales and crusts gives these feet and legs a strange appearance — as if they were made of crackled porcelain with pink glazing.

Open ulcers, about 2 ½ cm in diameter, are seen over both Achilles tendons and on the lateral margin of the right foot.

While there is free mobility in the hip- and knee-joints, only very slight and shaky movements can be performed in the ankle- and toe-joints. The knee-jerks are normal, and no definite sensory disturbances can be demonstrated.

Besides the above-mentioned changes in the skin of the extremities, the skin of the forehead and nose is thin and atrophic.

*X-ray Examination of the Skull:* Distinct moderate wavy hyperostosis of the anterior part of the frontal bone. The calvarium is thickened, with



Fig. 4.

diffuse sclerosis of the parietal part. Sella turcica normal. Facial bones deficient in lime salts (Fig. 5)

*X-ray Examination of the Extremities:* Large-meshed structure of the long bones with thinning of the corticalis, small areas of rarefaction here and there. A few small deposits of lime salts in the soft parts.

The changes commence in the proximal part of the forearms and a little proximally to the middle of the femur, increasing in intensity distally. They are very pronounced in the tibiae and feet, where the skeleton is extremely poor in lime salts. The diaphysis of the 5<sup>th</sup> metatarsal on the right side shows a rather large defect with irregular edges (Fig. 6).

*X-ray Examination of the Vertebral Column:* Moderate halisteresis. Pelvis normal. Extensive calcification of the aorta.

*Laboratory Examinations:* Hemoglobin, 70 %. Color index 1.08. White blood count 11,500. Red and white blood pictures normal.

Standard metabolism: 98 %—82 %. Serum calcium: 9:1 mg %. Serum phosphorus: 3.67 mg %. Serum phosphatase: 299 units.

Fasting blood sugar: 218 mg %—161 mg %.

Glycosuria: On admission, 0.7 %; later, 0.

Diacetic acid/acetone: On admission, +/0; later 0/0.

Spinal fluid: Cells 0/3; albumin 7; globulin 0.

Wassermann in blood and spinal fluid negative.

Electrocardiogram normal. Blood pressure: 160/90—170/80—140/70.

Hormonal analysis: Gonadotropic hormone 30 R.U. per day,

Estrin 20 M.U. " "

Testicular hormone 0 CCU.

*Eye Examination:* Secondary cataract of the right eye. Mature cataract of the left.

*Laryngoscopy:* Cartilaginous skeleton very protruding, especially in the arytaenoid region, owing to atrophy of the submucosa and mucosa. No sclerodermic changes in the vocal cords, which are freely movable.

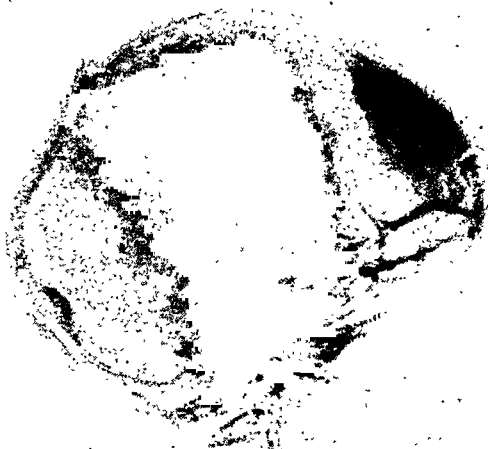


Fig. 5.

*Gynecological Examination:* Uterus small; otherwise no anomaly.

*Epicrisis:* The patient is a woman, 43 years old, who began to emaciate at the age of 5 years, and at the same time her growth began to be retarded. Her development is partially arrested, and she becomes somewhat infantile physically and mentally. All the tissues of the extremities undergo atrophy, especially the muscular and adipose tissue, but also the bones. The muscular power is minimum. Sexual maturity normal. The hair of the patient begins to get grey early. From the age of 27, sclerodermia develops on the feet and legs which subsequently become the site of ulceration and supuration.

From the age of 35—36 the vision is failing, and cataract appears, first on the right eye, later on the left.

At the age of 38 the presence of diabetes and frontal hyperostosis is ascertained.

*Present Positive Findings:* Grey hair, but infantilism, mental and physical;

almost complete atrophy of the musculature of the extremities;

distinct frontal hyperostosis and pronounced halisteresis of the distal bones of the extremities and of the facial bones;

monstrous sclerodermic changes in the skin of the feet and legs, and atrophy of the skin of the face and hands;

bilateral cortical cataract;

atrophy of the laryngeal mucosa;

blood sugar concentration of about 200 mg %

serum phosphatase 299 units (Lundsteen and Vermehren u.)

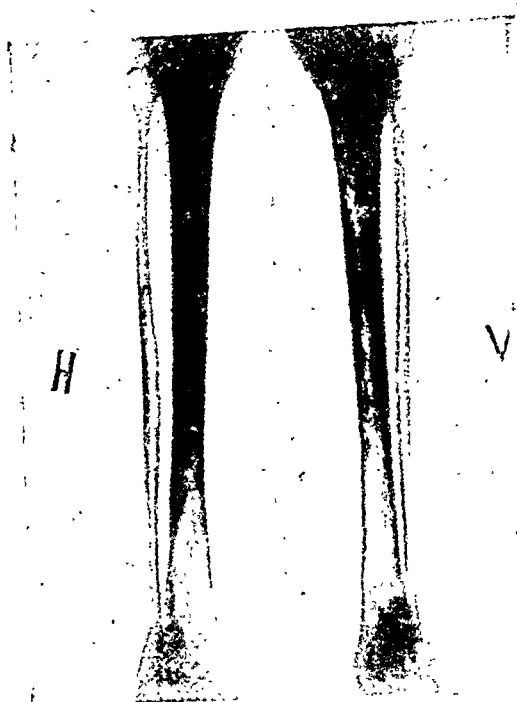


Fig. 6.

### Discussion.

This peculiar mosaic of symptoms and findings forms a nosographic picture that has been described in the literature under the name *Rothmund's disease*. In 1868 Rothmund noticed as the first this strange combination of cataract and skin lesion in a boy, 5 years old and in 3 other children in the same family, and gave a detailed description of his findings in a paper entitled: »Über Cataracten in Verbindung mit einer eigenthümlichen Hautdegeneration«.

Only few cases of this kind have been observed since. In 1930 Mamou collected 30 cases from the literature, and the latest account accessible to me reckons with a total of 32 cases (Agatston & Gartner, 1939).

Oppenheimer & Kugel (1934) point out that there is *no* resemblance between the cases reported by Rothmund and the cases subsequently described in the literature, and they raise doubt as to whether it be the same disease at all.

What Rothmund described is a »Marmorierung der Haut»,

appearing in the form of delicate red lines and a diffuse reddish color already in the very first years of life, which develops into a marked stria formation, resembling that of pregnancy »so sehr, dass sich der Leser kaum durch irgend ein Objekt unserer Affektion so vergegenwärtigen kann als eben durch den Bauch einer Mehregebärenden». A little later, though as early as in the 4'—5' year cataract develops, but otherwise »zeigen sich die Kinder von guter geistiger und körperlicher Entwicklung, ausser Auge und Haut ist kein Organ des Körpers als erkrankte nachzuweisen.»

There is a distinct difference between this description and the one given by Werner (1904) and subsequently by several other authors (Barbot, 1925; Krebs, Hartmann & Thiebaut, 1930; Sezary, Favory & Mamou, 1930). In this nosographic picture, which might be designated as »Werner's syndrome», the cardinal symptoms are: marked emaciation with defective physical development, bilateral cataract and sclerodermia (not the stria formation mentioned by Rothmund) and early greyness of the hair, sometimes baldness.

Common to the two clinical pictures is the peculiar combination of cataract and skin lesion. An explanation of the discrepancy may be found perhaps in the fact that the patients observed by Rothmund were all children from 3 to 12 years old, so that it may be that in their cases the disease had not reached its complete manifestation.

In his »Klinisk Endokrinologi», which often is very instructive when we are faced by the multitude of endocrine lesions, Herman Nielsen mentions also the symptomatology of this disease (vol. III).

The disease may manifest itself at any age although it commences preferably in childhood and in youth. Long before the appearance of the cataract and sclerodermia — which since Rothmund's report stand out as the signal features of the syndrome — the premature greyness of the hair may turn out, even as early as at the age of 8 years (Oppenheimer & Kugel). Also the emaciation is an early symptom.

The cataract is always bilateral and cortical and in this it resembles not only the tetanic but also other endocrine cataracts as encountered in acromegaly, diabetes insipidus, diabetes mellitus, etc.» (Herman Nielsen).

The sclerodermia alters the skin in a typical manner known from other lesions in which it is found as a symptom. The skin becomes atrophic, adherent to the underlying structures, hard, stiff and rough; but the refractory suppurations and ulcerations make it differ from other forms of sclerodermia. In some cases, as in the one presented here, poikilodermia is predominant with variegated pigmentation, teleangiectases, and keratotic flakes.

A characteristic feature of the disease is the synchronicity of infantile and juvenile features indicating an arrest of development and other symptoms as greyness, of the hair, depositing of lime salts in the vascular walls and atrophy of tissues, criteria of a premature senility, which at a first glance may be suggestive of progeria or Simmonds' syndrome.

It should be noted that in practically all the cases reported consanguinity and hereditary disposition have been pronounced features of the family history. Even Rothmund called attention to these features. 4 of his cases were found among the children of two families in which fathers and mothers were brothers and sisters. The 4 cases reported by Werner were found in one family. Other authors have reported that, besides the fully developed case, they had found other members of the family to present some isolated manifestation of the disease.

As mentioned in the case history our case appears to have been the only one of its kind in the family of the patient. With the kind assistance of Dr. V. Asschenfeld-Hansen I have obtained the information that 5 living sibs of the patient are healthy. They commenced to become grey-haired at the age of 40. There is no case of cataract or skin lesion in the family, nor any endocrine affection, nervous lesion, obesity, muscular impairment or other affection of the muscles — that is, an altogether negative family history.

As to the pathogenesis of the disease, several speculative hypotheses have been advanced. Rothmund thought the lesion involved a congenital anlage in the two organs, the skin and the lens of the eye, common to both. Also Oppenheimer & Kugel (1934) think that the cataract and the skin and hair changes are suggestive of a defect in the ectodermal anlage.

Some authors look upon the lesion as an endocrine disorder: parathyroid dysfunction (Mamou), pituitary affection (Von Arady).

As yet the foundation for the hypothesis about the parathyroid dysfunction is very slight. In a few cases the values obtained for serum calcium have been high, and in 1 case the authors (Oppenheimer & Kugel) found a negative calcium balance. A pronounced change in the calcium metabolism is evident in our case, however, in which we meet with sclerosis of the skull as well as pronounced halisteresis of the long bones, marked deposits of lime salts in the aorta and in the soft parts and extreme calcification of the aorta.

The features which in our case are directly suggestive of an endocrine disturbance as the cause of the lesion are found in the peculiar appearance of the patient, characterized by disturbances of the growth and development. This assumption finds support in the occurrence of cases which in addition have presented diabetes or a goiter with signs of hyperthyroidism.

In the case here presented we meet with diabetes mellitus, which was discovered rather late, at the age of 38. It has been rather severe, as is evidenced from the large dose of insulin required and from the acidosis demonstrated; still, it has been benign in its course insofar as it has not given rise to any attack of coma.

The frontal hyperostosis encountered in our patient is a finding the symptomatic value of which is still disputed, although gradually the majority of authors consider it to be of pituitary origin Bartelheimer (1939).

Mortimer (1938) has reported some extensive studies on dysplasia of the skull, based partly on experiments with hypophysectomized animals, partly on nearly 3000 roentgenograms of the skull of patients and in these he found a cranial type characterized by pronounced sclerosis of the calvarium, exostosis formation in the frontal part and infantile proportions — the same changes as encountered in the present case. In these patients Mortimer found signs of pituitary dysfunction; most of the patients were women with obesity, but all the patients who showed a pronounced hypoplasia of the skull were dwarfs. A similar cranial sclerosis could be produced in hypophysectomized rats and dogs by protracted administration of an alkaline pituitary extract. On the basis of these findings Mortimer thinks that sclerosis of the skull signifies a hypofunction of the pituitary gland.

Thus several findings are suggestive of an endocrine distur-

bance, perhaps a pituitary affection as the cause of the lesion, namely: cataract, infantilism, diabetes mellitus and frontal hyperostosis.

But, other features in the clinical picture presented by our patient point in another direction. Sclerodermia with ulceration, muscular atrophy, halisteresis of the long bones and depositing of lime salts in the soft parts are findings encountered as cardinal symptoms in several lesions: dermatomyositis, poikilodermatomyositis, and universal calcinosis.

For the present we have arrived at the clinical result that the present case of Rothmund-Werner's disease may be placed in relation to both the endocrine, especially pituitary, lesions and to the «sclerodermic group», as it presents a combination of symptoms of both kinds. The question then suggests itself whether there may be a causal connection between the two groups too. With our present, very limited, knowledge about the pathology of these diseases, however, this question will still have to be left open.

### Summary.

A case of Rothmund-Werner's disease is reported. Up until 1939 only 32 cases of this disease have been published (Agatston & Gartner).

The patient is a woman, aged 43, and the disease commenced at the age of 5 years with gradual emaciation and arrest of development. The patient has remained infantile physically and mentally — except for the sexual maturity which is normal.

There is pronounced atrophy of the muscular, adipose and osseous tissues of the extremities, also pronounced halisteresis. At the same time, there are extensive areas of calcification in the aorta and small deposits of lime salts in the muscles.

The hair of the patient turned grey at an early age.

At the age of 27, sclerodermia began to appear on the feet and legs, with subsequent characteristic chronic ulceration and suppuration. At the age of 35—36 years, cataract appeared, first in the right eye, later in the left.

At the age of 38, a rather severe degree of diabetes mellitus was ascertained, together with distinct frontal hyperostoses.



This case is the only one of its kind in the family of the patient, and isolated manifestations of the individual symptoms of the syndrome have not occurred in any members of the family.

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From the Pathological Department of the Copenhagen County Hospital, Gentofte (Chief Pathologist: A. Sæborg-Ohlsen, M.D.) and the Biological Department of Lovens kemiske Fabrik, Copenhagen.

## Thiouracil therapy in thyrotoxicosis.<sup>1</sup>

### Preliminary Report I.

By

JOHANNES THYSEN.

(Submitted for publication February 22, 1945).

The pathophysiology of the thyroid gland has long been a subject of great interest. The goiter problem has been studied thoroughly and some of its aspects have been clearly established but many questions are still left open, for instance, the etiology of hyperthyroidism. For none of the rather numerous theories advanced so far has proved adequate.

It is generally recognized that the direct cause of simple goiter is absolute or relative iodine deficiency. Under this condition the thyroid becomes hyperplastic in its attempt to produce thyroxin. Marine (1) (1931) states that the significance of the food elements as a strumogenic factor has long been recognized: a diet of swine liver alone may produce goiter in salmon, and excessive supply of oil-cakes gives goiter in cattle. In 1928 Chesney, Clawson & Webster (2) showed that a typical parenchymatous goiter develops in rabbits kept on a diet consisting almost exclusively of cabbage; and this observation was confirmed by Spence, Walker & Scowen (3)

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<sup>1</sup> Read before the Danish Society for Internal Medicine on May 21, 1944.

I wish here to acknowledge my indebtedness to the chiefs of the medical and surgical departments of the Copenhagen County Hospital, Gentofte — Professor Poul Morville, Dr. E. Rosling, Dr. M. Siggaard Andersen, Dr. O. Kapel, Dr. F. Wulff, and Dr. H. Wulff — for their permission to treat patients admitted to their departments and for their unbiased view concerning this treatment.

in 1932. Marine (1) states that press-cake of cabbage, from which 60 % of the juice has been pressed, has a strumogenic effect far greater than that of untreated cabbage. According to Webster (4) (1932), the effect of the factor here involved is considerably stronger than that of iodine deficiency, the strumogenic effect of the cabbage being entirely independent of the iodine content. Also other plants belonging to the same group (the brassica family) have the same effect, and rats react in this respect like rabbits (Hercus & Purves (5), Kennedy & Purves (6)). The changes in the thyroid are described as diffuse parenchymatous goiter, bringing about an increasing enlargement of the gland with hyperplasia of the parenchyma and loss of the colloid substance.

Several theories have been put forth to explain this particular effect on the thyroid, but no real advance towards an understanding of the mechanism here involved was made till 1941 when Griesbach (7) was able to explain coincidental histological changes in the anterior hypophysis, and Griesbach, Kennedy & Purves (8) showed that the strumogenic effect was dependent on the presence of the hypophysis.

Through experiments on rats with sulfaguanidine as intestinal disinfectant, Mackenzie, Mackenzie & McCollum (9) (1941) were able to demonstrate that also this substance has a strumogenic effect, giving similar changes in the thyroid as described above. These investigations were soon extended and Richter & Clisby (10) showed that also other sulphur compounds (phenylthiourea) had a similar effect. Independently of these investigations, Kennedy (11) found something similar for allylthiourea, as his findings made it probable that a derivative of thiourea was the strumogenic factor in rapeseed. After this, Astwood (12) (1943) examined the strumogenic effect and toxic action of 106 chemical compounds, including sulfanilamide and its derivatives. He emphasized that in particular two groups of substances — derivatives of thiourea and certain derivatives of aniline — had a strumogenic effect. The outcome of these studies was that thiourea and thiouracil (2-thio-6-oxypyrimidine) were the most effective and at the same time only slightly toxic. (For thiouracil the lethal dose was more than 100 times greater than the effective dose.)

Administration of thiourea or thiouracil to rats results in hyperplasia of the thyroid and a state of hypothyroidism with decrease

in the metabolism. Administration of iodine does not prevent this effect, whereas thyroxin prevents it. In keeping with this, it may be mentioned that administration of thiouracil to myxoedematous patients who at the same time are treated with dried thyroid substance does not prevent the increase in metabolism [Williams & Bissell (13)].

As mentioned, the histological picture of the enlarged thyroid shows glandular hyperplasia together with loss of colloid and resembles the histological picture encountered in thyrotoxicosis in man. Investigations reported by Marine (14) (1935) show, however, that this histological picture need not necessarily signify thyrotoxicosis; it may just as well mean that failure of the production of thyroid hormone has given rise to a compensatory increase in the output of thyrotropic hormone from the anterior pituitary.

The mode of action of the strumogenic substances has not been established clearly yet but that the point of the attack falls within the synthesis of thyroxin is evident from the following facts:

1. Thiourea and thiouracil given to rats produce goiter + hypothyroidism.
2. This effect is not prevented by administration of iodine.
3. On the other hand, this effect is prevented by simultaneous administration of thyroxin.
4. No goiter appears in hypophysectomized rats, but hypothyroidism develops.

In attempts to disclose the true mode of action of these substances, several investigators have employed radioactive tagged iodine in their experiments *in vitro*, and in this way they have been able to demonstrate that thiourea and many other thiocompounds have an inhibitory effect on the transformation of inorganic iodine to diiodotyrosin as well as to thyroxin [*e.g.*, Franklin & Chaikoff (15—16) (1943, 1944), Keston, Goldsmith, Gordon & Charipper (17) (1944), Schachner, Franklin & Chaikoff (18) (1944)]. It is emphasized that the inhibitory effect (of sulfanilamide) is dependent on the concentration of the substance. In keeping with this, Campbell, Landgrebe & Morgan (19) state that thiourea has a particular chemical affinity for iodine forming formamidine-disulphide-hydroiodide and thus preventing the synthesis of diiodotyrosin and thyroxin.

The substances mentioned (thiourea, thiouracil, etc.) appear not to occur in the organism under normal conditions, and an anti-thyroid effect of the kind mentioned appears not to play any role in the hormonal function of the normal thyroid gland. On the other hand, Carter, Mann & Jenkins (20) (1943) have demonstrated that paraxanthin (1—7-dimethylxanthin), which has an antithyroid effect, under normal conditions plays a role in the thyroid function in rats. In ox plasma the authors found the concentration of this substance to be 0.2—0.6 mg per cm<sup>3</sup>. This substance is able to inhibit the effect of thyroxine on a frog's heart; when given in optimal doses per os it is able to lower the basal metabolism in rats. Its effect depends decisively upon the proportion between this substance and thyroxine. The authors have found that for any given thyroxine concentration there is an optimal paraxanthine concentration which has a completely neutralizing effect; and they think that the metabolic rate in an animal is controlled by the proportion of thyroxine-paraxanthine. With balance in this proportion the metabolic rate will be low; an increase in either factor — from this state of balance — will increase the metabolism. Still the authors would not venture to advance the theory that variations in the paraxanthine content of normal animals is utilized by the organism for control of the metabolism.

From the observations cited and from theoretical considerations concerning the action of the strumogenic substances it seemed obvious to try the clinical employment of these substances in dealing with conditions of hyperthyroidism.

Astwood (12) who was the first to employ these substances in the treatment of patients suffering from thyrotoxicosis, states that here as well as in animal experiments it requires a certain latent period before a decrease in metabolism and the effect on the thyrotoxic symptoms appear. This latent period is due to the amount of thyroid hormone already formed and stored in the gland that has to be used up before the given substances may exert their effect. He emphasizes that it is a well-known fact that the reserve content of thyroid hormone is markedly reduced in hyperplastic thyroid glands, whereas a normal thyroid contains hormone sufficient to supply the organism for 1—3 months (man). In keeping with this, we found a latent period of 10—14 days in 3 patients with hyperthyroidism, whereas in 4 subjects with no

sign of hyperthyroidism he found no effect on the metabolism after such treatment for 2—4 weeks.

When various authors claim that the strumogenic substances have no effect on guinea-pig, the explanation of this will undoubtedly be that guinea-pigs with their histologically very inactive thyroid possess a rather large reserve stock of thyroid hormone at the same time as their consumption of it is relatively slight, and hence such experiments on guinea-pigs will have to be very protracted.

Astwood (12) found the effect of this treatment in cases of hyperthyroidism to be as follows: the thyrotoxic symptoms subside and the metabolism and serum cholesterol concentration return to normal levels. Subsequently, various papers have been published in rapid succession on the effectivity of thiourea and thiouracil in cases of hyperthyroidism [*e.g.*, Himsworth (21), Williams & Bissell (13) Frisk (22), Newman, Rienhoff & Rich (23)]. The results have been fairly uniform, consistent with those obtained by Astwood (12). Still, thiouracil appears to be superior to thiourea.

All told, the results appear very promising as to future treatment of thyrotoxicosis. Himsworth (21) even says that the results are so excellent that it seems safe to state that in these substances we have obtained therapeutically effective remedies for the treatment of thyrotoxicosis that are superior to anything available hitherto.

It soon turned out, however, that in many patients this treatment also had an untoward effect. Thus Astwood (12) found a transitory condition of agranulocytosis in a patient treated with thiouracil. Newcomb & Deane (24) have given an account of a case in which a severe degree of thrombopenia appeared under the treatment with thiourea. Welshman (25) treated 2 thyrotoxicosis patients with thiouracil and found leukopenia in both cases. In The Royal Society of Medicine, Himsworth (26) presented his results in 32 patients treated with thiourea and thiouracil; leukopenia developed in 2 of them, fatal agranulocytosis in 1; he distinguishes very sharply between overdosage of the remedy and idiosyncrasy. Of other, fairly frequent, by-effects mention is to be made of rise in temperature, nausea and vomiting (especially in thiourea therapy), skin eruption and increase in serum cholesterol to values over the normal limit [*e.g.*, Astwood (12), Himsworth (21), Johnson (27)].

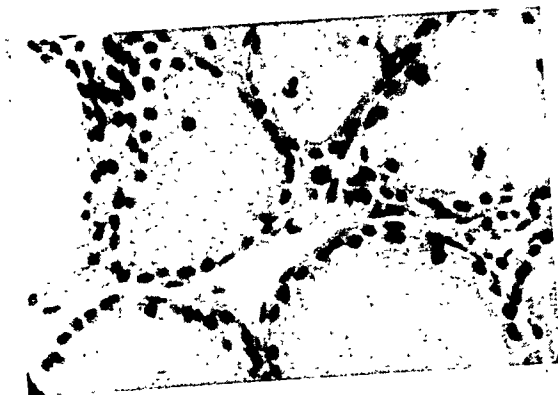


Fig. 1 a.

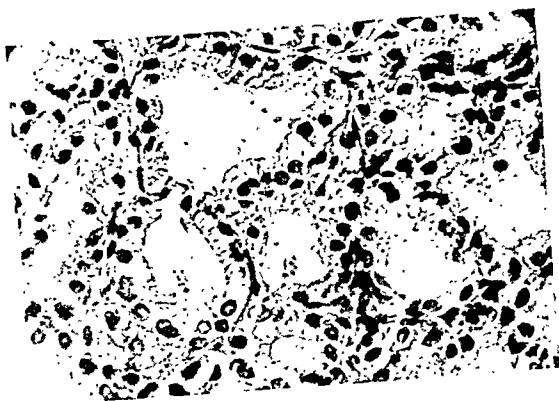


Fig. 1 b.

Haler (28) considers thiouracil a very dangerous remedy; he claims that fatal agranulocytosis from thiouracil therapy has been described at least in half a dozen cases; and he asserts that the substance should be employed only when the patient can be kept under a most exact control at the same time.

As to the dosage of these substances the statements differ a good deal. For thiourea the initial dose is about 1—3 g daily, for thiouracil about 1 g daily. As the most severe by-effects have appeared with the very high doses, however, there seems to be a distinct tendency to lower the dosage. When the effect on the thyrotoxic phenomena has made its appearance, the dose is decreased; when the remedy is discontinued, the symptoms reappear.

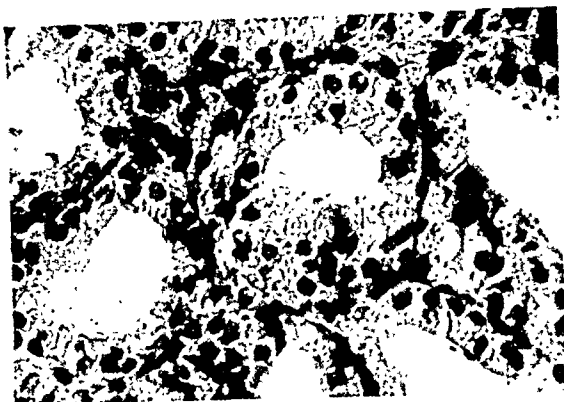


Fig. 1 c.

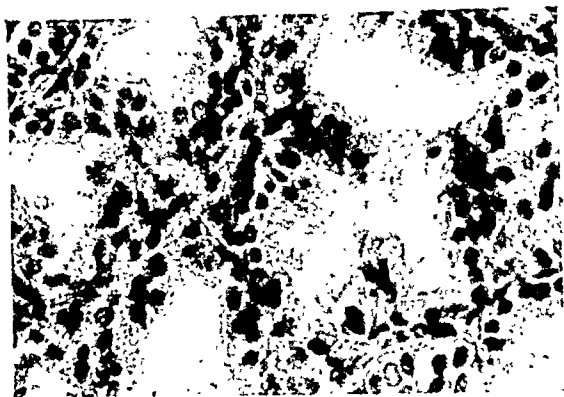


Fig. 1 d.

Fig. 1. Sections from thyroid glands of rats.

a, normal rat. b, rat treated with thiourea: 20 mg daily for 14 days. c, rat treated with thiouracil: 20 mg. daily for 14 days. d, rat treated with methylthiouracil: 10 mg daily for 15 days.

### Experimental Studies.

As a detailed account of my experimental studies will be given in a subsequent work, it will suffice here merely to mention a few outstanding points.

In determination of the minimal lethal dose the remedies were injected intra peritoneally on males rats, 6 months old, on two successive days (the easily soluble thiourea in aqueous solution, the nearly insoluble thiouracil in watery suspension). These experiments gave the following result:

Minimal lethal dose for thiourea: 1—2 mg,  
» » » » thiouracil: 375 mg.



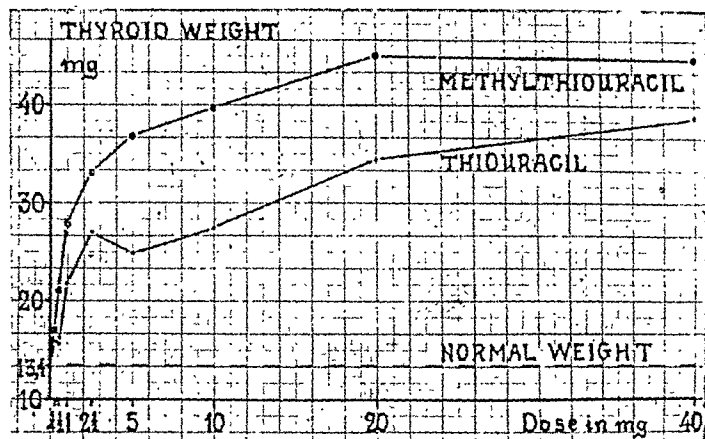


Fig. 2. Male rat, 6 months old, treated with thiouracil and methylthiouracil for 15 days.

Further, it was found that when thiourea was given by stomach tube in a dose of 10 mg a good many of the rats died in from some minutes to 6 hours after ingestion of this substance. On autopsy no mechanical injury was found to explain the death of these animals, whereas they all showed pronounced oedema of the lungs and marked bilateral hydrothorax. This is quite in keeping with the findings reported by Fraënkel (29): that a derivative of thiourea — allylthiourea — in animals produces anesthesia and death from pulmonary oedema and hydrothorax.

As the experimental studies further show that the strumogenic effect of thiourea in rat is less than that of thiouracil (Fig. 1), I have not tried at all to employ thiourea for therapeutic purposes, only thiouracil.

However, experimental biological studies on various substances closely related to thiouracil gave the result that in rats the strumogenic effect of *methylthiouracil* is considerably greater than that of thiouracil (see Figs. 2 and 3) and that the toxicity of this substance does not differ very much from that of thiouracil (minimal lethal dose for methylthiouracil: 325 mg), on which account I have also tried its employment in the clinic. A detailed account of the clinical results obtained with this substance will be given in a subsequent paper, which also will bring an attempt at a comparative estimate of the therapeutic effect of thiouracil and methylthiouracil

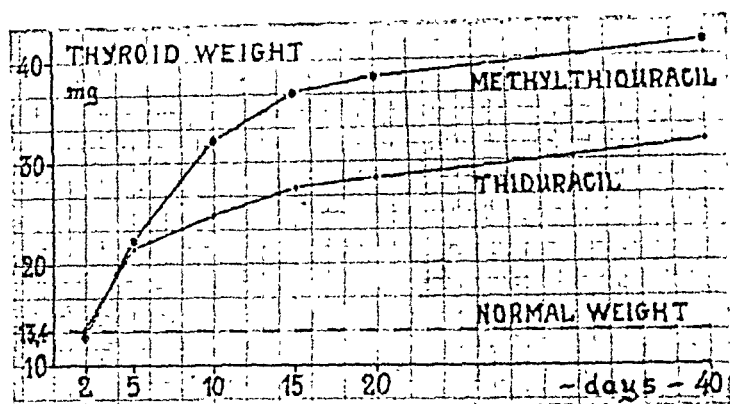


Fig. 3. Male rat, 6 months old, treated with 10 mg thiouracil and 5 mg methylthiouracil daily.

As the outcome of the biological experiments it is to be mentioned that they gave no result that might be taken to constitute an objection to the therapeutic employment of thiouracil and methylthiouracil in thyrotoxicosis, whereas thiourea appears to be far less suitable for this purpose. Further, a strumogenic effect has been demonstrated for several other, more or less near-related, substances, among the more effective of which the following are to be mentioned:

- 4.5-dimethylthiouracil (2-thio-6-oxy-4.5-dimethylpyrimidin),
- 4-methyl-5-ethylthiouracil (2-thio-6-oxy-4-methyl-5-ethylpyrimidin),
- 4-phenylthiouracil (2-thio-6-oxy-4-phenylpyrimidin).

Of these substances, phenylthiouracil proved to have the strongest strumogenic effect, and its toxicity was found to be very low (minimal lethal dose: 400 mg), on which account its clinical employment was tried too — in a case of moderate thyrotoxicosis. As will be shown in the following paper, however, the outcome of this experiment did not encourage to further therapeutic employment of the substance even though it by no means was ineffective clinically.

### Clinical Material.

In the medical and surgical departments of the Copenhagen County Hospital, Gentofte, since February 1944 altogether 12 thyrotoxicosis patients have been treated with thiouracil, and 28

with methylthiouracil. In the following paper an account will be given of the results obtained with methylthiouracil.

Of the 12 patients treated with thiouracil 9 had exophthalmic goiter, 1 thyrotoxic adenoma, 2 hyperthyroidism.

Of these patients 11 were women, 1 man. Their age varied from 31 to 69 years.

The average period of treatment for 6 of these 12 patients is now 288 days. 4 patients were submitted to operation after respectively 19, 53, 67 and 279 days of treatment with thiouracil. In 2 cases the thiouracil therapy was discontinued after respectively 30 and 157 days, whereafter the patients were given X-ray treatment.

For the sake of space, with the exception of two instances, the individual case histories will not be cited here in detail. As a matter of fact, the anamnestic data on the patients include no features of particular interest.

### *Grouping of the Patients.*

A. In 2 cases the treatment with thiouracil was partly or completely ineffective.

1. Woman, aged 63. *Diagnosis:* Hyperthyroidism; Mitral stenosis (compensated); Nervousness. Metabolism: + 20. Treatment with thiouracil — 20 cg  $\times$  6 daily — for 1 month gave no change in the metabolism, and the fairly mild thyrotoxic symptoms remained unchanged. After this, the administration of thiouracil was discontinued, and X-ray treatment was given. Half a year later, the thyrotoxic symptoms had subsided somewhat, but the metabolism was still + 20.

2. Woman, aged 68. *Diagnosis:* Hyperthyroidism; Angina pectoris; Nervousness. Metabolism: + 34. The patient was treated with thiouracil for 157 days — 20 cg  $\times$  6 daily, decreasing to 20 cg  $\times$  4 daily. Under this treatment her condition improved periodically, when the thyrotoxic symptoms subsided partially, and the metabolism fell to 100. But the symptoms reappeared, and the metabolism rose again to about + 20. As this happened repeatedly, and the treatment on the whole had no decisive effect, the thiouracil therapy was discontinued, and X-ray treatment was given.

B. In 8 patients the thiouracil therapy had a decisive effect on the state of thyrotoxicosis [7 patients with exophthalmic goiter, 1

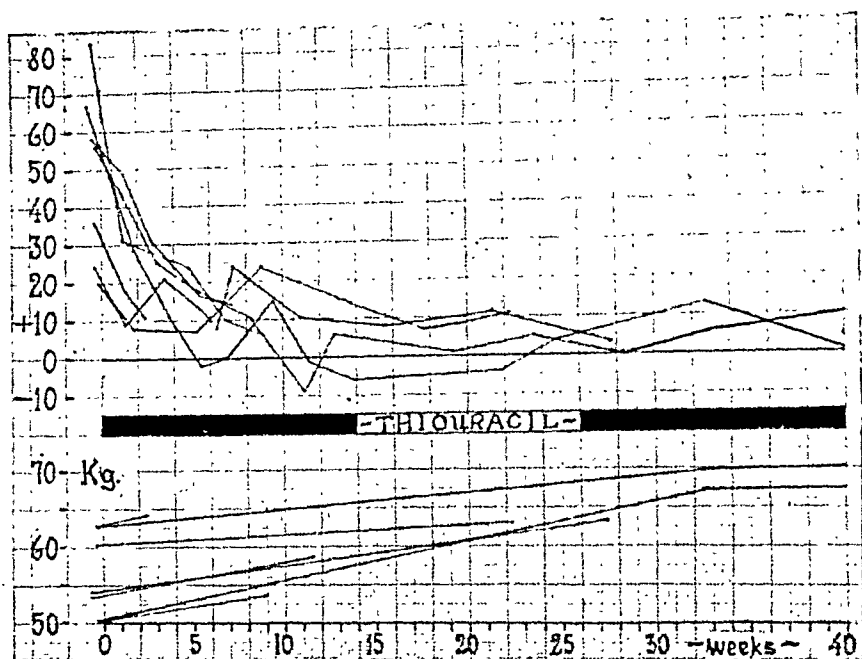


Fig. 4. Weight and metabolism curves for 7 thyrotoxicosis patients treated with thiouracil.

with hyperthyroidism (nodular goiter)]: the thyrotoxic symptoms subsided, the pulse rate fell to a normal level, the metabolism too, and the patients gained in weight (Fig. 4).

Of these 8 patients 2 were operated on, with good result. The remaining 6 patients are still under ambulatory treatment with thiouracil in small doses — after an average of 40.8 days' treatment with this remedy in the hospital. For the sake of control, at intervals of 3–8 weeks the patients are readmitted to the hospital for one day. In one of these cases, however, the thiouracil medication had to be discontinued because of an intense rash and oedema of the skin; but a few weeks later this patient tolerated methylthiouracil very well. The therapeutic results are still to be looked upon as satisfactory: the patients are able to work and apparently free from thyrotoxic symptoms.

In one of these cases (Fig. 5), after the metabolism had fallen to  $-12$ , the weight had increased and the thyrotoxic complaints disappeared, the thiouracil therapy was discontinued tentatively. Then the metabolism increased again, the weight fell off, and the

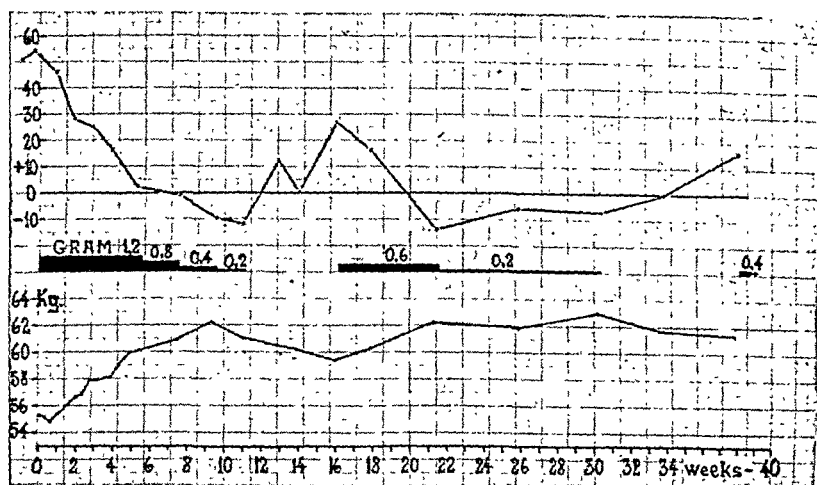


Fig. 5. Weight and metabolism curves for one of the patients under discontinuous treatment with thiouracil.

thyrotoxic symptoms reappeared. Under renewed treatment the condition of the patient became good again, but the same story repeated itself when the remedy was discontinued once more.

### C. The following 2 cases require particular mention:

1. Man, aged 63. Past history essentially negative. He had had a large goiter for about 10 years, but it had never inconvenienced him till lately. During the last 2 months before admission he had increasing thyrotoxic complaints. He entered the hospital on February 1, 1944. For 6 weeks he was treated with iodine and diiodo-tyrosine (Fig. 6) but without any effect: the metabolism kept at a level between +50 and +60, and the thyrotoxic symptoms remained unchanged. Then the iodine therapy was discontinued, and treatment with thiouracil was instituted. This was followed promptly by an intense acute aggravation of his condition: the rate of metabolism rose, the weight fell off, and the thyrotoxic features became pronounced, with weakness, tiredness, sweating and frequent diarrhea. The pulse rate, on the other hand, kept fairly constant, 70—80; the heart action became irregular, of the perpetua type. As the metabolism under continued treatment decreased but slowly, the thiouracil dose was increased — with the result that the metabolism rose again, and the state of the patient was further

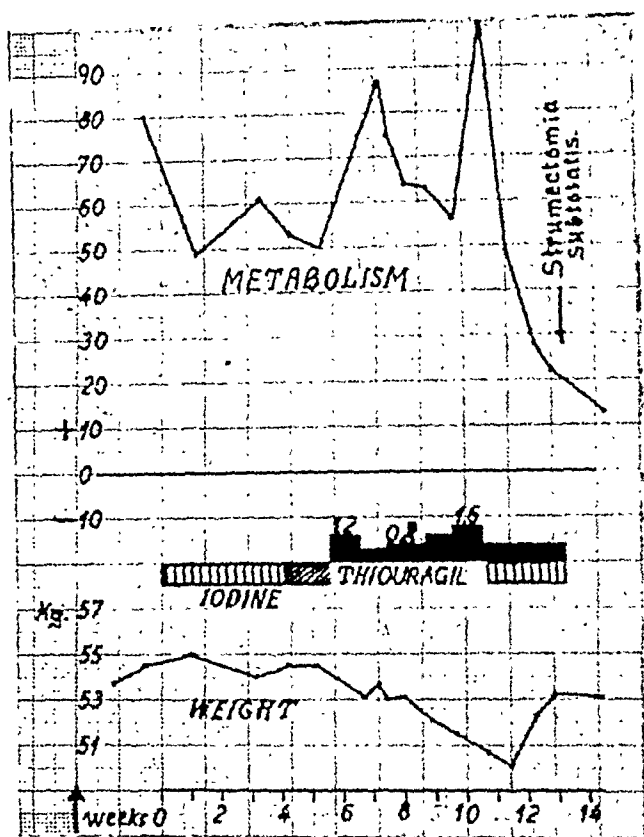


Fig. 6. Weight and metabolism curves for a male patient with thyrotoxicosis, treated with iodine and thiouracil.

aggravated. When now the thiouracil dose was decreased and iodine was given at the same time, a complete change took place in the patient: there was a great fall in the metabolism, the weight increased, and the thyrotoxic symptoms subsided slowly. After this, operative treatment was carried through without any difficulty.

2. Woman, aged 40. Past history essentially negative. Her thyroid affection commenced in July 1942 with rapidly progressing thyrotoxic symptoms. She was admitted to the hospital in July 1942. Protracted treatment with iodine and sedatives did not improve her condition, and the metabolism rose to a level between +80 and +100. On this account, as a last resort, an attempt was made at thymectomy (no thymus tissue was found) with the result that a violent thyrotoxic crisis set in. The patient was given varying doses of iodine for a total of 14 months, interrupted only by two

pauses of 12 and 42 days respectively. No therapeutic measure had any effect. Among other things, for a long time she was given large doses of vitamin A (40,000—80,000 I.U. daily) and also vitamin B<sub>1</sub> and B<sub>2</sub> (Becoplex, 2 cm<sup>3</sup> daily). In addition, for 29 days she received large doses of estrin (Ovex, 50,000 I.U. daily). Finally, X-ray treatment was tried too.

The condition of the patient persisted in being so poorly that operative treatment seemed too risky. Gradually, with the continuous thyrotoxicosis, she became extremely emaciated, completely cachectic (see Fig. 7). The subcutaneous tissue became leathery, thick and stiff; contractures of the lower extremities appeared; and the weight fell to 36 kg (weight on admission, 55 kg).

In this course of her illness the patient had a few better periods, but at no time was she able to stand an operation. The metabolism kept almost constantly between + 50 and + 100. Gradually there appeared a pronounced dilatation of the heart, auricular fibrillation, cardiac insufficiency with hydrothorax, enlargement of the liver, and oedemas.

In January 1944 the rate of metabolism was + 37 and + 44, the lowest level observed so far. In this period there was also an improvement of the general condition of the patient, but in February the metabolism rose again to a level above + 50 %. On February 26, 1944 administration of thiouracil was commenced (see Fig. 8), and this was followed immediately by a considerable aggravation of her condition. The patient seemed almost moribund. Still, this treatment was continued, and after about a week of it, the condition of the patient began to improve. This improvement has continued since, leading to an almost miraculous change in the state of the patient (see Fig. 7): the thyrotoxic symptoms disappeared, the marked exophthalmus subsided greatly, the weight increased from 36 to 56 kg and the metabolism showed a steadily decreasing tendency (see Fig. 8). The contractures relaxed, and the patient got up on June 10, 1944, feeling well and being able to walk about with the aid of a cane. Then she was discharged from the hospital, but readmitted 9 weeks later for the sake of operative treatment. In a following paper the operative result will be discussed in detail; here it will suffice to mention that the patient did not react at all to the operation: the pulse rate did not rise above 76 after the operation, and the temperature not above 38°.



Fig. 7 a.



Fig. 7 b.

Fig. 7. Woman, aged 40, with thyrotoxicosis.  
a, after  $1\frac{1}{2}$  years' ineffective hospital treatment.  
b, after  $5\frac{1}{2}$  months' treatment with thiouracil (see the text).



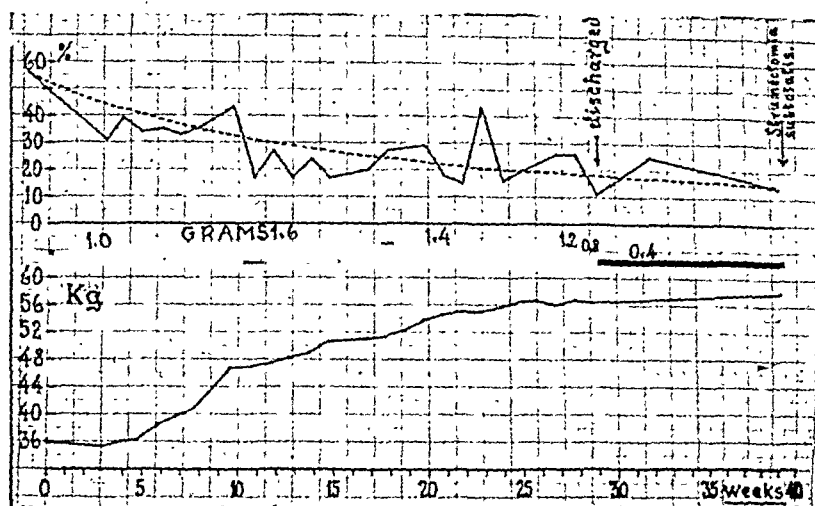


Fig. 8. Weight and metabolism curves for the patient shown in Fig. 7.

The therapeutic result in the last-mentioned case needs no comment. It speaks for itself, and it shows that in thiouracil we have a remedy which, in cases of thyrotoxicosis that prove refractory to any other form of treatment, is of decisive — nay, life-saving — importance.

A feature common to the 2 last-mentioned cases is that both patients were treated with iodine and both reacted to the institution of thiouracil therapy with an acute aggravation of their condition. The significance of the iodine treatment in connection with thiouracil and methylthiouracil therapy will be discussed in a following paper.

### *Dosage.*

In all the present cases the initial dose has been 1.2 g thiouracil daily — 1 tablet of  $20 \text{ cm}^3 \times 6$  daily. In a few cases the dose was increased subsequently to 1.6 g daily, which has to be looked upon as a rather large dose. The daily dose is decreased as the thyrotoxic symptoms subside and the pulse rate and metabolism return to normal values. The maintenance dose employed in these cases has been  $\frac{1}{2}$ , 1 or 2 tablets daily, or 1 tablet every 2—3 days, depending on the requirement of the individual patient.

It may be appropriate here to repeat that we consider methylthiouracil more serviceable than thiouracil in the treatment of

thyrotoxicosis, on which account we now use this remedy exclusively when the treatment of new patients is instituted. For this reason the dosage of methylthiouracil will be dealt with in the following paper.

### *Untoward Effects.*

As mentioned already, several authors have observed severe by-effects from this treatment which in some cases have resulted in the death of the patient. In contrast hereto, in our material there have been no serious by-effects whatever, although we have employed essentially the same dosage as is given in the foreign literature. It is to be emphasized that in one case (see Fig. 8) we employed a large dosage — 1.6 g daily for 13 weeks — without seeing any suggestion of untoward effects. The incidence and character of by-effects observed have been as follows:

<i>By-effects</i>	<i>No. of patients</i>
Transitory nausea .....	1
Bitter taste in the mouth .....	1
Transitory rise in temperature .....	2
Rash + oedema of the skin .....	2

### *Laboratory Examinations.*

At the same time as the patients have been under close observation with a view to the possible occurrence of untoward effects, each patient was submitted fairly regularly to various examinations in order to see whether a protracted administration of the remedy might disturb the internal milieu of the organism in other respects. Possibly the inhibitory effect of thiouracil on the synthesis of thyroxin is of anti-enzymotic nature (30). As yet, however, it is impracticable to say whether this effect is specific as to the synthesis of thyroxin, although several things point in that direction.

*Urine:* Albumin has not been demonstrated in the urine under this treatment.

*Hemoglobin %:* No abnormal deviations.

*Sedimentation Rate:* No abnormal deviations.

*Differential Count:* Of the 12 patients 7 showed a brief relative lymphocytosis. 4 patients showed a more protracted relative lymphocytosis, but this subsided too. The granulocyte count was never found to be less than 1000 per mm<sup>3</sup>.

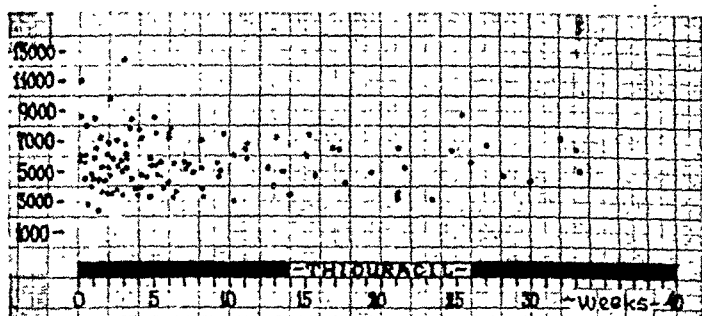


Fig. 9. White blood counts under treatment with thiouracil (12 patients).

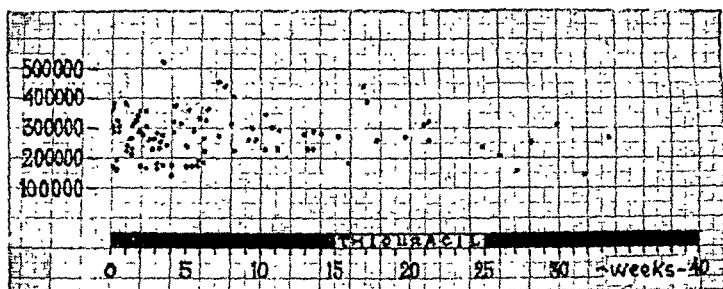


Fig. 10. Thrombocyte counts under treatment with thiouracil (12 patients).

*Sternal Puncture:* This was performed on altogether 5 patients after 1—2 months of treatment. The examination of the punctates, obligingly performed by Dr. A. Sæborg-Ohlsen, Chief Pathologist, showed an increased activity in the erythrocytic or leucocytic system, or in both, but otherwise no abnormality.

*White Blood Count,* see Fig. 9.

*Thrombocyte Count,* see Fig. 10.

*Fasting Blood Sugar Concentration,* see Fig. 11.

*Blood Urea,* see Fig. 12.

*Serum Calcium,* see Fig. 13.

*Serum Cholesterol,* see Fig. 14.

Only the serum calcium and serum cholesterol determinations give rise to any comment. Fig. 13 illustrates that the values for serum calcium after 10 weeks' treatment with thiouracil show a rather considerable dispersion; several values lie at a level of about 8.5 mg %, and 3 patients show low values ( $< 8$ ). In one of these

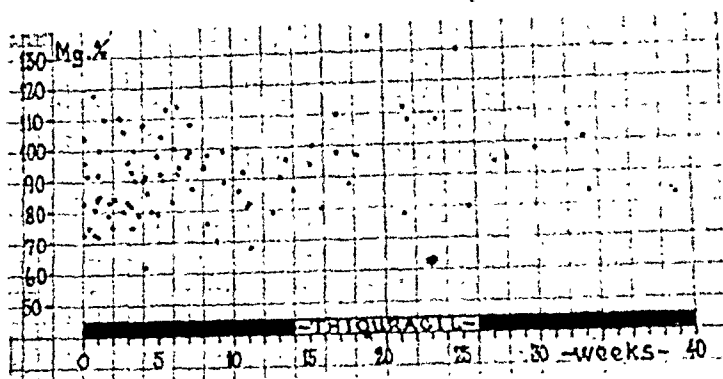


Fig. 11. Blood sugar determinations under treatment with thiouracil (12 patients).

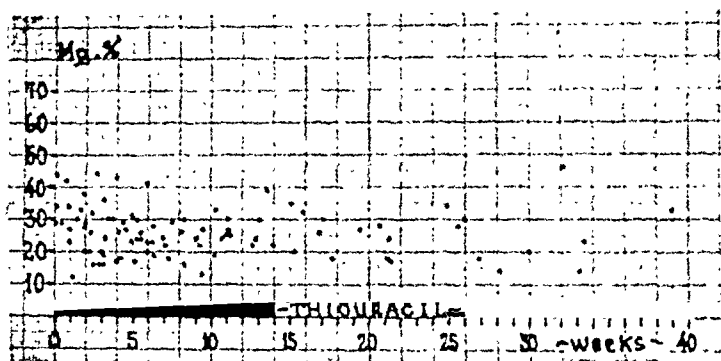


Fig. 12. Blood urea determinations under treatment with thiouracil (12 patients)

cases the thiouracil therapy was discontinued at this point of time; in the other two patients the values rose later on. Even though no definite clinical symptoms of hypocalcemia were found in the patients, it cannot be excluded that thiouracil may have some effect on the parathyroid glands, on the production of the parathormone. This question is now being investigated more thoroughly.

Fig. 14 confirms the statement made by other authors: that the serum cholesterol concentration, which often is very low in patients with thyrotoxicosis, increases under the treatment with thiouracil. Only a few determinations of this kind have been made, it is true, but the values obtained appear to indicate that this rise — sometimes to values far above the normal — is merely transitory.

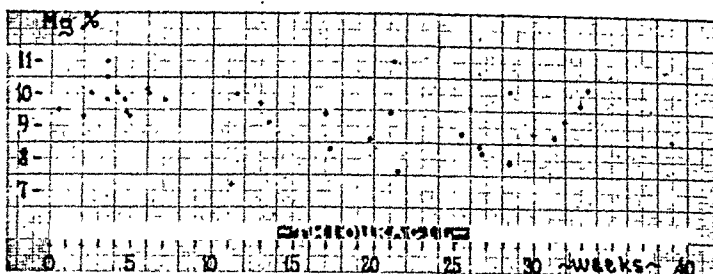


Fig. 13. Serum calcium determinations under treatment with thiouracil (11 patients).

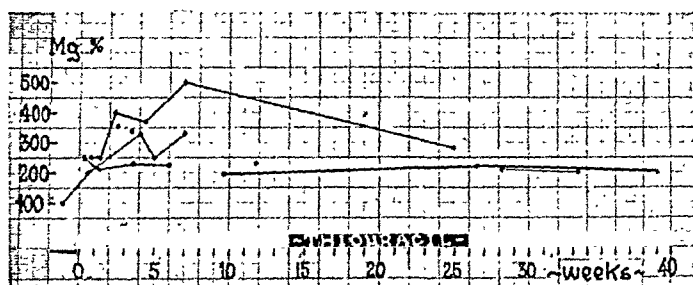


Fig. 14. Serum cholesterol determinations under treatment with thiouracil (7 patients).

*Size of the Goiter:* In addition, by measuring regularly the circumference of the neck of the patients we have tried to estimate roughly whether the treatment with thiouracil brought about any change in the size of the goiter present. Although this form of examination is very rough it still gives a hint in this respect.

Of 7 patients examined,

- 1 showed a decrease in the size of the goiter,
- 2 » no change » » » » » ,
- 4 » an increase » » » » » .

*Exophthalmus:* This phenomenon was present in 4 of the 12 patients. In 1 it remained unchanged under the treatment, in the remaining 3 patients the exophthalmus disappeared partially or completely (see Fig. 7).

The question about the treatment of thyrotoxicosis with thiouracil and methylthiouracil will be discussed further in the following paper.

### Summary.

After a review of the present literature on the action of strumogenic substances in experimental animals, the clinical employment of thiourea and thiouracil is dealt with.

From his own experimental studies the writer emphasizes that the toxicity of thiourea is very great in comparison to that of thiouracil (about 1:375), while its strumogenic effect is considerably smaller, on which account thiourea is considered unserviceable for clinical purposes.

It is further pointed out that methylthiouracil has a greater strumogenic effect than has thiouracil, whereas the toxicity of the two substances is fairly alike.

After this, an account is given of the treatment of 12 thyrotoxicosis patients with thiouracil. In this material the longest period of treatment is 11 months. The therapeutic effect on the thyrotoxic symptoms appears after a latent period, which is prolonged considerably by treatment with iodine and as a rule leads to apparently complete disappearance of the symptoms. Only in 2 patients has the therapeutic result not been satisfactory. Four patients were operated on with good results; 6 patients have been given thiouracil therapy for an average period of 288 days, with satisfactory result. No serious by-effects have been observed, only a few instances of nausea, rise in temperature and exanthema.

Under this treatment no noxious effect has been noticed on the hemoglobin percentage, sedimentation rate, blood urea or blood sugar concentration, and no instance of albuminuria has been demonstrated. None of the patients have shown thrombopenia, nor has a granulocyte count under 1000 per  $\text{mm}^3$  been observed. Sternal puncture has shown an increase in the erythrocytic and myelocytic systems. The treatment has brought about a considerable, though apparently merely temporary, rise in the serum cholesterol values and fall in the serum calcium values.

The treatment appears to bring about a decrease in the exophthalmus, but no tendency to a reduction in the size of the goiter; and there is nothing till now to indicate that the treatment has a curative effect. When the treatment is discontinued the symptoms reappear.

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From the Medical Clinic of the Serafimer Hospital, Stockholm.  
(Head Physician: Prof. A. Kristenson).

## **Seasonal variations in morbidity in cases of gastric ulcer and duodenal ulcer.**

By

**THOR SÄLLSTRÖM, M. D.**

(Submitted for publication November 29, 1944).

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The view has long been held that there is a certain periodicity in attacks of gastric and duodenal ulcer and in the resultant trouble, in that there is found to be an accumulation of patients suffering from ulcer and ulcerous trouble during certain seasons of the year. By periodicity is thus meant here not merely the more or less intermittent course of the disease but its recurrence at various times of year.

Statements in literature on this seasonal variation are not always in full mutual agreement; this is due to a number of factors. The variegated composition of the research material is undoubtedly one of the most important of these factors. For instance, the material is sometimes surgical, sometimes medical. Moreover, different principles have, of course, been applied to a certain extent in passing judgment on the cases, especially in earlier years, when the diagnosis was only clinically determined and not based on X-ray examination. Again, such literature as exists on the subject is mostly of somewhat out of date.

Many authors, however, have observed and described a similar seasonal variation in the morbidity of ulcers. It may be said, on the whole, that there are two prevailing views. One group of authors states that an increase in ulcerous cases is observable



during the winter months—December—February (Gebhardt-Richter, Mattisson, Moynihan, Ruszuyak and others). On the other hand, there are authors who describe an accumulation of ulcerous attacks and ulcerous trouble in the autumn and spring — here the frequency is generally said to reach its peaks during September—November and March—May (von Bergmann, Cohnheim, Ellinger, Einhorn, Hutter, Kalk, Katsch, Schütz etc.)

These seasonal variations occur in cases of both gastric and duodenal ulcer (Gebhardt-Richter, Hutter, Mattisson, among others). Some authors, however, consider that the periodicity is far more pronounced in duodenal than in gastric ulcers (Cohnheim, Hutter, Schütz, etc.)

Although such statements in literature are frequently somewhat divergent, it may certainly be said that a factor common to them all is that the summer months show a minimum and the autumn-winter months a maximum of the disease.

Those who work in a medical policlinic also gain a strong impression of this seasonal fluctuation. It appears to me that insufficient attention is paid to these conditions, and as it is, of course, not impossible that this very variation in frequency may be of importance in the genesis of ulcers, I have considered myself justified in again drawing attention in this short paper to the seasonal variations in the morbidity of ulcers.

In order to try to gain some idea as to whether it is possible from a modern body of material of *ulcus ventriculi* and *ulcus duodeni* to demonstrate a periodicity in the frequency, I have carried out an investigation of the ulcer material covering the last few years at the Serafimer Hospital. The composition of this material has been published by me in an earlier paper, which provides evidence that on the whole the present material agrees with earlier ulcer material published in literature. It is thus quite an ordinary and in no way peculiar body of material relating to ulcerous cases that has served as a basis for the following enquiry. At the same time, however, I would point out here that *all cases of ulcer in my material have been subjected to X-ray diagnosis.*

During the period 1937—42 altogether 656 cases of gastric and duodenal ulcer were treated at the medical clinic of the Serafimer Hospital. This material has been investigated in respect of the occurrence of the disease throughout the 12 months of the year.

Table 1.

The date of diagnosing gastric and duodenal ulcer during the period 1937—42.

Year	Jan.	Feb.	Mar.	Apr.	May	June	July	Aug.	Sept.	Oct.	Nov.	Dec.	Total
1937	5	7	6	10	5	5	8	3	9	9	7	10	84
1938	4	5	6	2	8	5	2	2	10	12	5	5	66
1939	4	5	6	6	3	0	3	6	11	3	4	5	56
1940	7	14	6	9	4	4	2	8	16	12	8	18	108
1941	12	18	14	11	12	5	3	9	19	18	16	6	143
1942	21	24	14	21	8	12	7	14	16	26	18	18	199
	53	73	52	59	40	31	25	42	81	80	58	62	656

The easiest method is to divide up the cases according to the time of year at which disease was diagnosed, this period generally coinciding closely with date of admission to hospital (see Table 1).

When an opinion is formed of the seasonal variations in a certain disease, it is generally this very type of division of the cases that sheds a light on the subject. The table also shows clearly that the number of treated and diagnosed cases of ulcer is considerably lower during the summer months May—August than during the rest of the year. There is a minimum frequency in June and July and a maximum frequency in September and October.

It is, however, not the time at which the disease is diagnosed that is of any particular interest so much as the time at which the disease arose. As a rule, however, it is impossible to determine the date of emergence of a gastric ulcer or a duodenal ulcer, for it is characteristic of an ulcer that the disease is preceded by more or less lengthy periods of stomachic trouble. On the other hand, one frequently obtains relatively exact data as to when a palpable deterioration in the disease sets in. For one finds in a great many patients that they usually suffer from an acute increase in the trouble for a varying period before the disease is diagnosed. In the majority of cases the anamnesis reads as follows: »The patient has had periodical gastric trouble in recent years, but a month ago it distinctly grew very much worse.» Generally, that is to say, the patient is able to indicate more or less exactly when he became distinctly worse. Obviously the date when he grew worse is of greater

Table 2.

The date when the trouble first became aggravated in cases of *ulcus ventriculi* and *ulcus duodeni* during the period 1937—42.

Year	Jan.	Feb.	Mar.	Apr.	May	June	July	Aug.	Sept.	Oct.	Nov.	Dec.	Total
1937	6	2	3	8	6	3	6	7	3	10	3	8	65
1938	6	5	2	3	4	4	2	6	14	7	2	3	58
1939	3	9	5	5	2	2	3	7	4	5	5	4	54
1940	11	7	4	12	2	7	12	11	10	8	8	9	101
1941	7	10	10	8	9	7	4	15	12	9	8	13	112
1942	16	16	13	11	11	6	9	15	15	16	19	20	167
	49	49	37	47	34	29	36	61	58	55	45	57	557

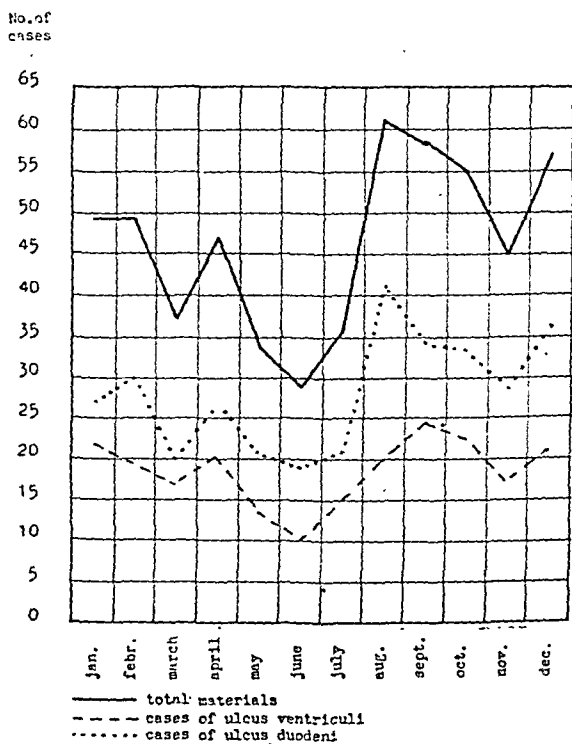


Fig. 1. When the trouble first became aggravated in cases of *ulcus ventriculi* and *ulcus duodeni* during the period 1937—42.

interest in this connection than the date on which the disease was diagnosed.

In the present material, therefore, the anamneses have been carefully studied and the date of a more definite deterioration in health determined. Though this has not been successful in every case, it has in most, and the table 2 gives the figures obtained, the result being indicated in graphic form in Fig. 1.

It is also possible to read from this table a manifestly lower frequency in respect of the disease during the months May—July, whereas the number of cases increases during the autumn. Compared with the preceding table we see that the conditions have shifted, the minimum now lying in June and the maximum in August—October.

Here, then, we observe without any doubt a seasonal variation in the frequency of ulcer. We then ask ourselves whether this variation only affects ulcer or whether it is a more common phenomenon applying to other diseases as well. In order to gain some idea of this we must have a body of comparative material. The material from a policlinic will suit admirably as a means of registering the general morbidity as far as hospital cases are concerned. For this purpose, then, I have examined the policlinic material accumulated in the medical policlinic at the Serafimer Hospital in the years 1940—42 and have studied its dispersion throughout the different months of the year (see table 3).

Here we can read approximately the same conditions obtaining as just now in the case of ulcer, viz. that a manifest, even striking difference exists between the winter and the summer months — a circumstance of which those who work in a policlinic are no doubt universally aware. That is to say, the general morbidity recorded in hospital material presents striking seasonal variations.

If, now, we compare the seasonal variations in the case of ulcer with those in the general morbidity observable in my policlinic material, it is seen that the curves do not tally exactly. Thus, the minimum for the general morbidity lies in September, whereas the ulcer frequency is lowest during May—June, and the maximum for the general morbidity lies at the beginning of the year, while that in the case of ulcer is observed at the close of the year.

During the period 1937–42 there were diagnosed at the medical policlinic at the Serafimer Hospital 1,397 cases of ulcer. During

Table 3.

The no. of cases of illness at the medical policlinic at the Serafiner Hospital in 1940—42 and the no. of treated cases of ulcer during the period 1937—42.

	Jan.	Feb.	Mar.	Apr.	May	June	July	Aug.	Sept.	Oct.	Nov.	Dec.	Total
Cases of illness at med. pol. (a)	6112	6007	6714	6745	5354	5308	5497	5400	4853	5324	5886	4733	6793
No. of treated cases of ulcer (b)	49	49	37	47	34	29	36	61	58	55	45	57	557
b in % of a	0.80	0.81	0.55	0.69	0.63	0.54	0.61	1.13	1.19	1.03	0.76	1.20	0.82

the same period the cases of ulcer treated at the hospital numbered 656, i. e. about 50 % of those diagnosed at the policlinic. During half that period, i. e. 1940—42 there were examined at the policlinic about 70,000 cases. It is self-evident that the ulcer cannot to any great extent influence the seasonal variations in the main group representing the general morbidity. It is permissible, therefore, with some justification to let the policlinic material serve as comparative material for the purpose of studying whether the seasonal variations are more pronounced in the case of ulcer ventriculi and ulcer duodeni than in the general morbidity. For that purpose I have calculated the percentage relation between the monthly figures for ulcer frequency and those for the general morbidity; these may be studied in table 3. It makes no difference for our purposes here that the general morbidity is based on a 3-year period and the ulcer frequency on a 6-year period (where half the period corresponds to that covered by the general morbidity), provided we remember that the ratios thus obtained do not express the ulcer frequency in relation to the policlinic material. The average for this ratio works out at 0.82 %. It can be seen that in January, February and November the ratio ranges around the average, while for the other months considerable variations upwards and downwards are observable. This may mean that the ulcer morbidity is subject to more pronounced seasonal variations than the general morbidity.

If we select 2 groups, e. g. one group comprising the 3 summer months and one group comprising the 3 autumn months, where in the first case the ulcer frequency is low and in the second case higher, while the groups are otherwise more or less uniform, we can study the conditions statistically with the aid of the figures in the table.

In the months of May, June and July during the years 1940—42 16,159 patients were examined. In the corresponding months of 1937—42, 89 cases of ulcer were treated at the hospital. The ratio between these figures is 0.55 %. The corresponding figures for the period August, September and October are: 15,577 polyclinic patients and 174 ulcer patients with the ratio 1.12 %. There is thus a striking deviation between the ratios in the first and in the second group. A statistical calculation works out as follows:

$$e(M_1) \text{ in the first group is } \pm \sqrt{\frac{0.55 \times 99.45}{16159}} = \pm 0.059$$

$$e(M_2) \text{ in the second group is } \pm \sqrt{\frac{1.12 \times 98.88}{15577}} = \pm 0.084$$

In the first group, then, we get the ratio  $0.55 \pm 0.059$  and in the second group  $1.12 \pm 0.084$  %. We can at once see from this that there is a marked divergence. The difference between the ratios, which is 0.57 %, is far greater than 3 times the mean error of the respective groups.

Working out the mean error for the difference, we get:

$$e(D) = \pm \sqrt{0.059^2 + 0.084^2} = \pm 0.102.$$

From this it is clear that the difference is far greater than 3 times the mean error for the differences, from which it follows that in all probability the demonstrated divergence cannot be due to accidental causes.

We are thus able to prove that the ulcer morbidity is subject to more marked seasonal variations than the general morbidity in this material, so that the ulcer frequency is lower in the summer and higher in the autumn.

No difference has been observable between the conditions in ulcer ventriculi and those in ulcer duodeni. The different curves for ulcer ventriculi and ulcer duodeni are drawn in Fig. 1, where

Table 4.

Showing the time when the trouble became aggravated in cases of *ulcus ventriculi* and *ulcus duodeni* that had been diagnosed for the first time.

Jan.	Feb.	Mar.	Apr.	May	June	July	Aug.	Sept.	Oct.	Nov.	Dec.	Total
34	23	27	25	19	18	16	37	31	31	19	29	309

it can be seen that possibly *ulcus ventriculi* does not show the same rapid rise in the autumn as *ulcus duodeni*, though on the whole the curves follow one another fairly closely.

The material relating to *ulcus* that has been discussed here comprises all the cases of *ulcus*, even, that is to say, cases of relapse. As it may be objected that cases of relapse in this connection are not pure cases, I have separated them, the figures thus obtained being given in table 4. As will be seen, no appreciable difference is observable.

Another question that may arise when dealing with material such as that from the Serafimer Hospital, into which sometimes city dwellers and sometimes country people are admitted, is whether any difference can be observed in this respect between patients from the country and patients from the city. A division of the cases into these categories indicates that the number of country-folk is proportionately far less than the number of urban patients — only 169 out of 656. The number of cases is thus quite small, and if spread over the 12 months of the year we get of course only relatively uncertain values. Here, however, we cannot find evidence of any definite divergence between the seasonal variations in patients from the country and those from the town.

Our discussion has related throughout to those cases of *ulcus ventriculi* and *ulcus duodeni* which have been treated at the medical clinic. One important source of error that affects such material from the Serafimer Hospital when it is to be scrutinized and judged, as we are doing here, is the fact that during the summer months the clinic closes one ward at a time for cleaning. This reduces the number of hospital beds by about 40 during the months of June, July and August, though usually not the whole of June or the whole of August. It is obvious that, if there is no

Table 5.

The no. of cases of *ulcus ventriculi* and *ulcus duodeni* diagnosed in the medical polyclinic at the Serafiner Hospital in 1937—42.

Jan.	Feb.	Mch.	Apr.	May	June	July	Aug.	Sept.	Oct.	Nov.	Dec.	Total
131	129	123	115	96	77	86	90	113	171	156	102	1.309

room for patients during certain months of the year, the number of cases of *ulcus*, as of all other pathological cases, during that period is bound to be relatively smaller than at other times of year, when the hospital is working to full capacity. In order to study in what manner this source of error affects the result which I have obtained above, I have worked out the number of cases of *ulcus ventriculi* and *ulcus duodeni* that were diagnosed at the polyclinic during the period 1937—42, and these numbers are given in table 5.

There is no demonstrable external influence upon the number of visitors to the polyclinic. This table also shows that there is a distinct difference between the figures for *ulcus* frequency in the summer months and those in the winter months. If, however, we compare this table with, for instance, table 1, we see that the treated cases, i. e. those admitted to hospital, in proportion to the number diagnosed show a somewhat variable ratio. On an average, between 40 and 50 % of the diagnosed *ulcus* cases are admitted to hospital. In some months this frequency is higher, e. g. during February, September and December, while in other months it is lower, e. g. during July and November. There is thus a not very easily explainable variation in the ratio between diagnosed and admitted cases of *ulcus*. When it comes to explaining the low frequency of admitted cases of *ulcus* in July, it may be asserted with some degree of probability that this is due to the reduced number of hospital beds during that months. This circumstance might possibly, therefore, be a source of error when associating the seasonal variations with the frequency of *ulcus*. If we study the same periods as above: May, June and July in comparison with August, September and October and raise the number of treated cases in the former periods so that the treatment frequency comes



to about the same for both periods — the estimated figures obtained are 120 and 203 respectively — we get a ratio between the number of patients visiting the polyclinic and the ulcer cases, which in the first period is  $0.74 \% \pm 0.067$  and in the second period  $1.29 \% \pm 0.042$ , i. e. there is here too a variation so wide that it cannot merely be due to an accident.

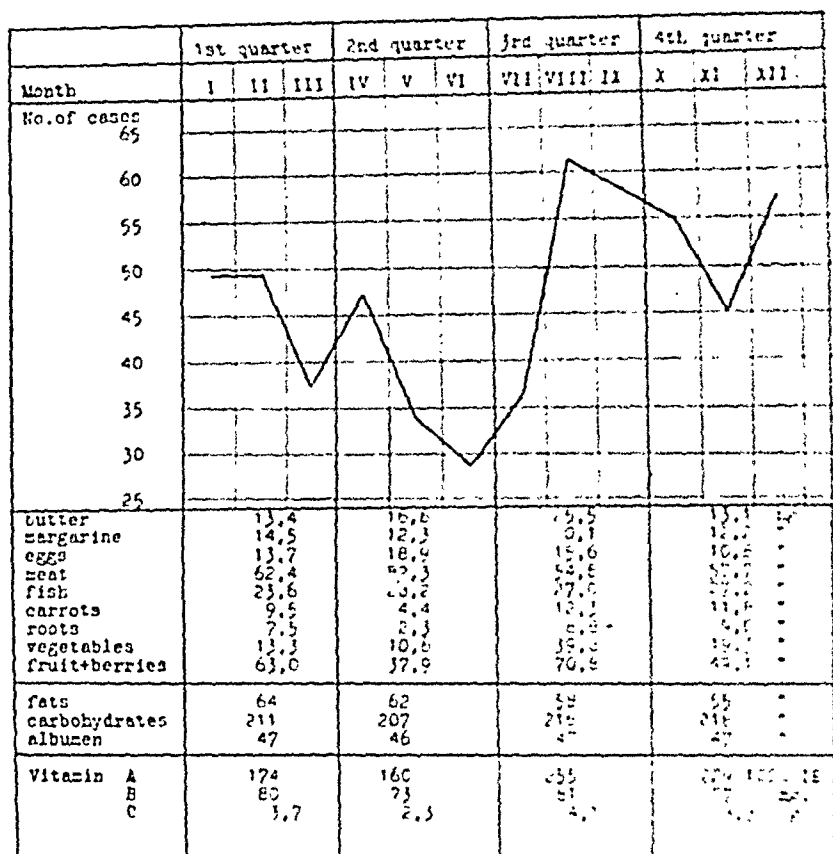
There occurs, then, in the material which I have studied a manifest seasonal variation. Different views have been expressed in literature as to the causes of these seasonal variations. The main conditional factors suggested have been catarrhal affections (Mattisson, Einhorn) and dietetic conditions (Mattisson, Einhorn, v. Bergmann and Katsch). von Bergmann and Katsch, for instance, are of the opinion that vegetables in the spring and fruit in the autumn are factors to be taken into account, and they point out, *inter alia*, that in calves one not infrequently finds duodenal sores at the time of transition from milk food to raw fodder. Others, however, have also suggested the effects of the weather on the individual (Mattisson, Ellinger, v. Bergmann and Katsch, Gebhardt and Richter). Ellinger, who associates himself with von Bergmann's theory of the importance of vegetative stigmatization in ulcer, regards the patients' increased sensitiveness to light as important. Sun-rays, declares Ellinger, increases the ventricular secretion and motility in the spring and autumn, and this increase is checked in the summer by the heat. Ruszuyak has also demonstrated the existence of a hypersecretion and a hyperacidity during the months of May and October. Endocrin causes are likewise believed to have some significance; Cohnheim actually considers that the entire cause is to be found in the dependence of the human individual upon the oestral periods.

The views on the causes of the seasonal variations are many and various, it is clear, and this shows that so far we have made no progress in this field of enquiry beyond sheer guesswork. Indeed, it is difficult, of course, to progress beyond that. Those factors with which we are here concerned are hardly capable of exact determination.

The Royal Social Board has made an investigation into the consumption of food in the major towns in this country, and there are statistics relating to the variation in the consumption of different foods during the four quarters of the year. It may be of interest

Table 6.

Figures taken from «Household budgets & food consumption» published by the Royal Social Board. Above the table is drawn the ulcer frequency curve recorded in my investigations.



to compare this variation with the seasonal variations in ulcus. It would naturally have been best if we could have obtained particulars of the ulcer-patients' manner of living during the period before they fell ill, but such data have been unobtainable. In table 6, however, I have reproduced figures out of a table to be found in the Royal Social Board's publication «Hushållsbudgeter och livsmedelskonsumtion i städer och tätorter 1940—1942» (Household budgets and food consumption in towns and densely populated areas in 1940—42). In my table I have only concerned myself with the year 1940, as it no doubt corresponds most closely with the consumption under normal conditions; moreover, I have only included

in the table those foodstuffs of which the consumption has demonstrably shown an appreciable variation according to the seasons. At the top of the table I have inserted the ulcer frequency.

Those quarters of the year which attract the greatest interest in the table are the 2nd qr. — on account of the slight frequency on ulcer in May and June — and the 3rd qr. — owing to the heavy rise in ulcer frequency in August and September. In the 2nd qr. we find an increase in the consumption of eggs and fish and a decline in the consumption of meat, carrots, vegetables, roots, berries, vitamins B and C. In the 3rd qr. we note an increase in butter, carrots, roots, vegetables, fruit, berries and vitamins A, B and C, and a falling-off in the consumption of margarine and eggs. In the last qr. of the year there is again a decrease in the consumption of butter, eggs, vegetables, fruit and berries. Thus, the consumption of carrots, vegetables, roots, fruit and berries is lowest during the 2nd qr., where too we find the lowest ulcer frequency. In the 3rd qr. the consumption of these same articles is at its maximum, just as we find here the maximum ulcer frequency. It is interesting to note that the consumption of vitamin A in particular is highest during the 3rd and last quarters and lowest during the 1st and 2nd quarters.

It is not, of course, my intention directly to attribute the ulcer frequency to these demonstrated variations in the consumption of food — and indeed the data obtained are so uncertain as hardly to warrant any opinion being given on the basis of them. I have merely desired to draw attention to the possibilities that are at present open to anyone studying these questions. Similar food investigations on the basis of ulcer material might possibly enable us to gain a clearer conception of the true nature of the conditions.

### Summary.

The enquiry has shown that ulcer ventriculi and ulcer duodeni exhibit manifest seasonal variations with a minimum frequency during May—June and a maximum frequency during August—September.

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Aus dem Medizinisch-Chemischen Institut der Universität Helsinki,  
Vorstand Professor, Dr. med. et phil. P. E. Simola. Aus der Panzer-  
brigade; Arzt Oberstabsarzt O. Kopperi.

## Über die durch Motorabgase verursachten Kohlenoxydvergiftungen bei der Mannschaft von Panzerformationen.

Von

LEO NORO.

(Bei der Redaktion am 2. Februar 1945 eingegangen).

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### *Einleitung.*

Die Kohlenoxydvergiftungen haben sich in den letzten Jahren in Finnland durch die mittels Holz- und Kohlevergasern getriebenen Kraftfahrzeuge entwickelt. Doch sind die Kohlenoxydvergiftungen nicht auch in früheren Jahren auf dem Autogebiet unbekannt gewesen. Noch mag man sich erinnern an die Vergiftungsfälle mit tödlichem Ausgang, die dann und wann in Garagen eintraten, in denen der Motor bei geschlossenen Türen in Betrieb gewesen ist. Gegenüber dem Treibstoff der Holz- und Kohlenvergaser-Kraftwagen, dem »Kohlengas«, das ca. 20—30 % CO enthält, umfasst das Abgas der Benzinmotoren ebenfalls ca. 6—10 % Kohlenmonoxyd (Baader, Rodenacker). Ein derartiger CO-Gehalt ist durchaus genügend, in einer schlecht gelüfteten Halle recht bald einen gefährlichen Kohlenoxydgehalt in der Respirationsluft zu verursachen. So beobachteten Stampe und Bangert bei ihren CO-Bestimmungen in Autohallen, dass z. B. ein kleiner Benzinmotor schon in 4 Minuten in einer  $5 \times 10 \times 3.6$  m grossen Halle einen auf 0.03 % steigenden CO-Gehalt und in  $\frac{1}{2}$  Stunde einen solchen von 0.15 % verursacht hatte. Bei denselben Versuchen erwies sich CO als sehr langsam verdunstend aus einer geschlossenen Halle: nach  $\frac{1}{2}$  St. war

davon noch 0.05 % in der Luft enthalten. Ein grösserer, 2000 cm<sup>3</sup>-Motor bewirkte nach einem Gebrauch von 25 Min. einen Gehalt von 0.28 Vol. %. Bringen wir diese Zahlen in der graphischen Darstellung Fig. 1 unter, in der wir die Wirkung des CO der Atmungsluft auf die CO des Blutes und Vergiftungssymptome sehen, so erkennen wir, dass die obengenannten Gehalte auch schwere Vergiftungssymptome bewirken können.

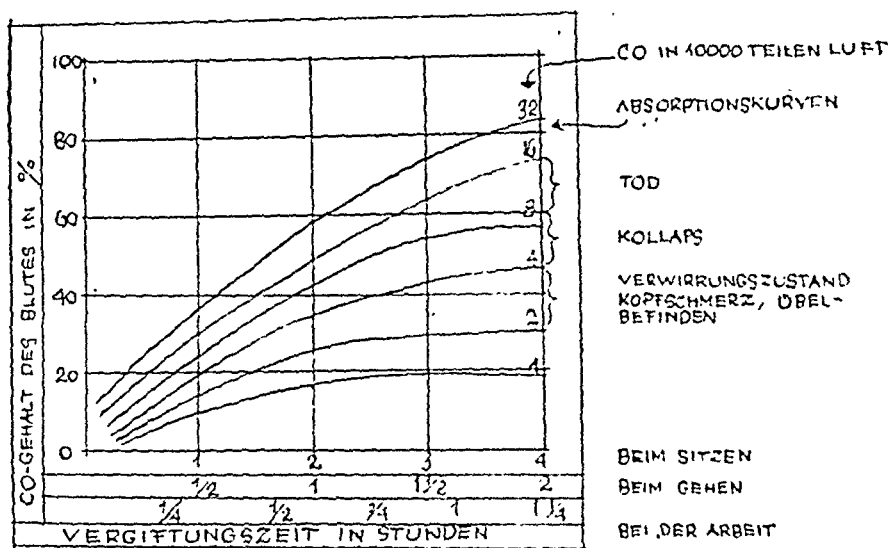


Fig. 1.

Die Wirkung von CO der Atmungsluft auf CO des Blutes und auf die Symptome.

Die Panzerwagen sind während dieses Krieges in Finnland hauptsächlich die Motoren gewesen, die fortgesetzt Benzin als Treibstoff benutzt haben. Doch hat auch ihr Brennstoff ausser Benzin einen bedeutenden Teil Motorspiritus enthalten, was meines Wissens keinen grösseren Einfluss auf den CO-Gehalt des Abgases ausgeübt hat.

Als ich in diesem Kriege über ein Jahr als Bataillonsarzt in der Panzerbrigade diente, erhielt ich durch meine dort angestellten Beobachtungen den Anlass zu den im folgenden darzustellenden Untersuchungen, deren Zweck es gewesen ist, die auf Abgasen beruhenden CO-Vergiftungen bei Panzermännern zu erforschen. Da die Untersuchungen unter technisch unvollkommenen Verhältnissen in der Feldarmee haben ausgeführt werden müssen, sind sie leider in gewissen Hinsichten unvollständig geblieben.

### Das Material.

Das Material enthält insgesamt 198 Panzersoldaten, darunter 45 Monteure, 88 Panzerfahrer und 65 Kraftwagenfahrer. Von diesen wurden für eine genauere Untersuchung 45 Fälle ausgesucht, bei denen akute und auf chronische Kohlenoxydvergiftungen hinweisende Symptome aufgetreten waren. Bei den Untersuchungen wurde den subjektiven Symptomen sowie bei den ausführlicher Untersuchten insbesondere neurologischen Symptomen, dem CO-Gehalt des Blutes und seinen Schwankungen in der Arbeitszeit, dem vollständigen Blutbild sowie dem Blutdruck Aufmerksamkeit zugewandt.

### Die Frequenz der Vergiftungen.

Auf die sehr vielseitigen Symptome, die bei den akuten und den chronischen Kohlengasvergiftungen auftreten, möchte ich in diesem Zusammenhang nicht näher eingehen. Sie sind unter anderen von Almgren, Baader, Noro, Rodenacker, Salén, Sibelius, Syman-ski u. a. ausführlicher beschrieben worden. Im folgenden haben nur die wesentlichsten von ihnen Beachtung gefunden. Bei den 198 Panzersoldaten, die befragt wurden, waren auf CO-Vergiftungen hinweisende Symptome folgendermassen aufgetreten: Tabelle 1 und 2.

Es ist zu ersehen, dass bei der Gruppe der Kraftwagenfahrer verhältnismässig am meisten und schwerste Vergiftungssymptome vorgekommen sind, was in erster Linie darauf beruhen mag, dass

Tabelle 1.

Auf akute Vergiftungen hinweisende Symptome bei 198 Panzersoldaten.

	Anzahl	Bewusst- los	Kopf- schmerz	Schwindel	Übelkeit	Symptom- los
Monteure .....	45	1	23	15	14	18
Panzerfahrer .....	88	5	51	27	33	30
Kraftwagenfahrer .....	65	6	40	29	25	23
Insges...	198	12	114	71	72	71
in % ..		6	58	36	37	36

Tabelle 2.

*Auf chronische Vergiftungen hinweisende Symptome bei 198 Panzersoldaten.*

	Anzahl	Ermüdung	Nervosität	Reizbarkeit	Schläfrigkeit	Abmagerung	Herzbe- schwerden	Atembe- klemmung	Uriniierungs- beschwerden
Monteure .....	45	7	3	2	1	2	3	7	3
Panzerfahrer .....	88	15	10	7	—	6	7	13	3
Kraftwagenfahrer ....	65	19	9	7	2	9	4	7	8
insges. ...	198	41	22	16	3	17	14	27	14
in % ..		21	11	8	2	9	7	14	7

sie im allgemeinen ältere Männer gewesen sind und längere Zeit mit Motoren zu tun gehabt haben.

Auf chronische Vergiftungen hinweisende Symptome sind nach Tabelle 2 aufgetreten.

Wir erkennen abermals, dass auch jetzt bei den Kraftwagenfahrern am meisten Beschwerden aufgetreten sind.

Vergleichen wir die Frequenz der Vergiftungen bei den Panzersoldaten mit der bei den Fahrern von Kraftwagen mit Holz- und Kohlevergasern (in Duodecim 1944 Nr. 6 ausführlicher von mir besprochen) so ist zu ersehen, dass die Vergiftungen bei jenen etwa halb so häufig wie bei letzteren sind.

### *Der CO-Gehalt des Blutes.*

Als ich sah, in welchem Masse der CO-Gehalt des Blutes während der Arbeit steigt, stellte ich nach Oettel's Methode am Morgen vor Beginn der Arbeit und gleich nach ihrem Abschluss CO-Bestimmungen am Blut an. Die Bestimmungsweise, die sehr einfach und auf das Stufenphotometer angewandt ist, erwies sich bei höheren Werten als genügend exakt. Wenn es sich um geringe Werte unter 5 % (d. h. das Verhältnis des CO-Hämoglobins zum Gesamthämoglobin) handelt, konnten die Werte indes bei Wiederholungsbestimmungen um bis 1—2 % schwanken. Aus der folgenden Tabelle (3) ersehen wir die im Verlaufe eines Tages eintretenden Schwankungen der CO-Werte des Blutes. Die Versuchspersonen waren alle Monteure.



Tabelle 3.

*Der CO-Gehalt des Blutes am Morgen und nach der Arbeit.*

Fall	Morgenwert %	Nach der Arbeit %	Gestiegen %
1	$\frac{1}{2}$	$11\frac{1}{4}$	$10\frac{3}{4}$
2	$2\frac{1}{4}$	$11\frac{3}{4}$	$9\frac{1}{2}$
3	$1\frac{3}{4}$	$10\frac{3}{4}$	9
4	$2\frac{1}{4}$	9	$6\frac{3}{4}$
5	$\frac{3}{4}$	$7\frac{1}{2}$	$6\frac{3}{4}$
6	2	7	5
7	$1\frac{3}{4}$	6	$4\frac{3}{4}$
8	0	$2\frac{3}{4}$	$2\frac{3}{4}$
9	2	$3\frac{3}{4}$	$1\frac{3}{4}$
10	1	$1\frac{3}{4}$	$\frac{3}{4}$
11	$1\frac{1}{2}$	2	$\frac{1}{2}$
12	1	0	—
13	$1\frac{1}{4}$	0	—

Wie bereits erwähnt, ist die Bestimmungsmethode *nicht genau* bei geringen Werten, so dass die Fälle 12 und 13 wohl dadurch erklärt werden können. Setzen wir voraus, dass ein über 5prozentiger CO-Gehalt im Blut für die Entstehung eines chronischen Vergiftungszustandes ausreicht (Salén), so erkennen wir bei der Durchsicht der Tabelle, dass bei 7 der in ihr aufgeführten Personen diese Bedingung erfüllt ist, wenigstens am Versuchstage.

Das Kohlenmonoxyd verdunstet schnell aus dem Blut, größere Mengen binnen zwei Stunden (Haldane). Doch hatte ich Gelegenheit, einen Fall zu verfolgen, in dem das CO des Blutes länger einen höheren Stand einnahm. Obgleich der in Frage stehende Fall durch einen Holzvergaser bedingt war, sei er hier beschrieben.

Es handelte sich um einen 22jährigen Fahrer, der in meine Truppenverbandplatz kam, weil er an auf chronische Vergiftung hinweisender Beschwerden litt. Der CO-Gehalt des Blutes wurde bestimmt, und er belief sich auf  $1\frac{1}{2}$  %. Unmittelbar darauf ging der Mann, den Generator seines Holzvergaser-Kraftwagens zu füllen, und er atmete das daraus aufsteigende Kohlendgas zu lange ein, wodurch er sich eine akute Vergiftung zuzog. Ihre Symptome waren Schwindel, Gefühl der Leichtigkeit, Kopfschmerzen und Husten. Der CO-Gehalt des Blutes belief sich, unmittelbar nach der Vergiftung gemessen, auf 15 %, aber er steigerte sich noch 15 Min. bei zunehmenden Kopfschmerzen auf 21 %. Danach durfte der

Patient in frischer Luft unhergehen, und 15 Min. nach der Vergiftung war der CO-Wert schon auf 16  $\frac{1}{4}$  % gesunken. Kopfschmerz und Schwindel bestanden fortgesetzt, die übrigen Symptome waren schon 1  $\frac{1}{2}$  Stunde nach der Vergiftung vorübergegangen. Die Kopfschmerzen setzten sich unverändert fort, und der CO-Wert des Blutes machte 14 % aus. Sie hörten erst nach 6 Stunden auf, und noch am folgenden Morgen enthielt das Blut 7 % Kohlenmonoxyd, trotzdem der Patient sich nicht mehr in kohlengashaltiger Umgebung aufgehalten hatte.

Der Fall erweist, dass CO aus dem Blut nicht immer so schnell verdunstet, wie man im allgemeinen annimmt.

### *Das Blutbild.*

Viele Forscher (unter anderem Forbes, Litzner, Symanski) erwähnen als wichtiges, ca. 25—30 %ig auftretendes Symptom bei chronischen CO-Vergiftungen Polyzythämie, die auch bei Tierversuchen ein regelmässiges Symptom gewesen ist (Nasmith und Graham, Tscherkess). Dieses Symptom kann sich nach Ziegler bisweilen sogar erst Jahre nach der Vergiftung entwickeln. Die Ursache der Polyzythämien erklärt Ziegler folgendermassen: »Sie beruhen auf einer krankhaft beschleunigten Zellreifung einem toxischen Angriff auf die Produktionsstätte des roten Knochenmarkes selbst.« Da wir uns jedoch an die zentrale CO-Wirkung insbesondere auf die Stammganglien und die Hypothalamusgegend erinnern, wo die zentrale Blutregelung zu suchen ist (Feuchtinger), möchte ich mich meinerseits Leschke anschliessen, nach dem die Veränderungen im Blutbild zentraler Art sind. Seltener sind als Symptome von CO-Vergiftungen auch Anämien angetroffen worden (Joss und Huber, Brandt, Beck und Fort-Ziegler), die dann ihrem Typ nach hyperchromisch, mit den bei Trotylvergiftungen angetroffenen hyperchromischen Anämien vielleicht genetisch übereinstimmend gewesen sind (Noro).

Nach Symanski tritt im weissen Blutbild keine für Vergiftungen spezifische Veränderung auf. Doch ist im Zusammenhang mit ihnen Monozytose, Eosinophilie und relative Lymphozytose vorgekommen.

Meine eigenen Beobachtungen betreffen 45 Panzersoldaten, die chronische Vergiftungssymptome aufgewiesen und als deren Kontrollen 12 anders betätigte Panzersoldaten gedient haben. Ausser diesen wurden an 2 akuten Vergiftungsfällen Beobachtungen angestellt.

Die Anzahl der *Erythrozyten* betrug nur in 8 Fällen über 5 Mill./mm<sup>3</sup> (bei einem Höchstwert von 5.30 Mill. je/mm<sup>3</sup>), so dass auch sie wohl noch nicht als deutliches Anzeichen von Polyzytämie gelten kann. In den übrigen Fällen schwankte die Anzahl der Erythrozyten von 4.52—5.00 Mill. Anämien sind nicht angetroffen worden.

Die Anzahl der *Leukozyten* variierte von 5000—10000 mm<sup>3</sup>, was als Normalwert anzusehen ist (Schulten, Nordenson).

Die Analyse der *Leukozyten* geht aus der folgenden Tabelle (4) hervor.

In der Mitte die als normal zu betrachtenden Werte.

Tabelle 4.

*Die Differenzierung der Leukozyten in 45 Fällen.*

	mehr .....	1
Segmentk.	50—70% .....	32
	wen. ....	12
	mehr .....	8
Stabk.	3—5% .....	15
	wen. ....	22
	mehr .....	6
Ly.	20—40% .....	34
	wen. ....	5
	mehr .....	10
Eos.	2—4% .....	16
	wen. ....	19
	mehr .....	20
Mon.	4—8% .....	23
	wen. ....	2
	mehr .....	1
Bas.	0—1% .....	44

Bei der Durchsicht der Tabelle ist zu ersehen, dass Abweichungen von den Normalwerten in beiden Richtungen wahrzunehmen sind. Nur bei den *Monozyten* scheint eine Abweichung nach grossen Werten vorherrschend zu sein. Sonstiges Sicheres über die Differenzierung der *Leukozyten* lässt sich nicht mit Sicherheit aussagen.

In zwei akuten Vergiftungsfällen konnte das Blutbild nach der Vergiftung verfolgt werden.

Der erste Fall war ein Soldat, der, erst einige Tage als Kraftfahrer tätig, durch einen mit Benzin getriebenen Wagen eine zur Bewusstlosigkeit führende Kohlengasvergiftung erlitt. Er wurde am Morgen in das Krankenhaus gebracht, und das am Abend aufgenommene Blutbild war folgendes:

Hb 84 %, E: 4.56, I: 0.92, L: 9700.

Und nach 4 Tagen, als er nach seiner Genesung das Krankenhaus verliess:

Hb 82 %, E: 4.48, I: 0.96, L: 6000.

Als einzige Abweichung können wir also die grössere Anzahl der Leukozyten am Vergiftungstage beobachten.

Der zweite Fall war ein Soldat, der 4 Jahre als Kraftfahrer tätig gewesen war und der auch früher schon oft akute CO-Vergiftungen erlitten und ausserdem chronische Vergiftungssymptome aufgewiesen hatte. Er zog sich dasselbe Mal wie der vorhergehende eine zur Bewusstlosigkeit führende Vergiftung zu. Das an demselben Abend aufgenommene Blutbild war folgender Art:

Hb 108 %, E: 5.34, I: 1.01, L: 10300.

Das 4 Tage später ermittelte Blutbild hatte sich auf folgende Weise in normaler Richtung verändert:

Hb 100 %, E: 4.88, I: 1.02, L: 6700.

Nach der Vergiftung besteht also eine leichte *Polyzytämie* und *Leukozytose*, die dann während der Genesungszeit schwinden.

Wollte man auf Grund dieser zwei Fälle die Erscheinungen irgendwie erklären, so könnte man unter anderen daran denken, dass das für die Regelung der Blutbildung des letzteren Mannes arbeitende Zentrum im Hypothalamusteil schon während der früheren Vergiftungen beschädigt worden wäre und beim Eintreten einer neuer Vergiftung empfindlicher als gewöhnlich reagiert hätte.

### *Blutdruck.*

Bei den chronischen CO-Vergiftungen ist auch ein Steigen des Blutdruckes als eines der Symptome aufgetreten. (Baader, Rodenacker.) Unter diesen 45 Fällen war er bei 5 über 150 mm Hg. Doch ist zu bemerken, dass in diesem Krieg bei den Soldaten oft hoher Blutdruck beobachtet worden ist (Ehrström), dessen Ursache man in psychischem Einfluss zu suchen hat. Daher ist es auch in diesen Fällen unmöglich zu sagen, ob der hohe Blutdruck gerade auf der CO-Vergiftung beruht, besonders wenn zugleich keine anderen auf Vergiftung hinweisenden objektiven Symptome zu beobachten sind.

### *Nervensymptome.*

Die Symptome auf seiten des Zentralnervensystems sind sowohl bei akuten als auch bei chronischen Kohlengasvergiftungen höchst mannigfaltig. Beschreibungen darüber finden sich unter anderem in den Veröffentlichungen von Sibelius und Almgren.

Bei meinen eigenen Fällen wurden als einzige objektive neurologische Symptome ein ziemlich starker Tremor in 6 Fällen beobachtet. Otoneurologische Untersuchungen konnten leider nicht ausgeführt werden.

### *Besprechung der Ergebnisse.*

Betrachten wir eingangs auf Grund dieser Bemerkungen die Frequenz der Kohlendgasvergiftungen bei der Mannschaft der Panzerformationen, so können wir sagen, dass die Vergiftungen ziemlich allgemein gewesen sind. Im Vergleich zu den durch die Holz- und Kohlenvergaser-Kraftwagen verursachten Vergiftungen (Noro) sind sie jedoch in meinem Material etwa halb so häufig wie letztere und ihrem Charakter nach stets gelinde gewesen, was insbesondere die chronischen Vergiftungen angeht. Bei den Panzerformationen scheinen insbesondere die Kraftwagenfahrer am meisten unter Kohlendgas zu leiden, was wohl daran liegt, dass sie im allgemeinen am längsten auf dem Motorgebiet gearbeitet haben.

Im CO-Gehalt des Blutes sind in den meisten Fällen sogar bedeutende Anstiege während der Arbeitszeit, Mehrbeträge, die bis 10 % ausmachen können, zu beobachten.

Im Blutbild sind keine ganz charakteristischen Veränderungen zu erkennen, wenngleich in dem roten Blutbild eine Tendenz zu Polyzytämie und im weissen als einziger übereinstimmender Zug Monozytose bestanden hat. Doch ist in Betracht zu ziehen, dass alle Fälle gelinde gewesen sind, so dass auch keine grösseren Veränderungen im Blutbild haben erwartet werden können. Ebensovienig sind im Blutdruck deutliche Veränderungen, abgesehen von 5 Fällen, hervorgetreten.

Als kurze Zusammenfassung können wir also feststellen, dass bei der Mannschaft der Panzerformationen etwa bei jedem zweiten Mann CO-Vergiftung aufgetreten ist, doch ist sie im allgemeinen sehr gelinde gewesen.

### **Summary.**

The purpose of the examination has been to clarify the commonness of CO-poisoning in men serving in armoured car units. The material consists altogether of 198 men, of whom 45 were more closely polyclinically examined. The most common subjective sym-

ptoms in acute poisonings have been headache (58 per cent), sickness (37 per cent), dizziness (36 per cent). Unconsciousness has appeared in 6 per cent of the cases. The most common symptoms indicating chronic poisonings have been fatigue (41 per cent), sleepiness (27 per cent) and irritability (17 per cent). The CO-contents of the blood could arise during the work to as much as 10  $\frac{3}{4}$  per cent. It has been observed that the only uniform symptom in the changes of the blood picture is monocytosis and in a case of acute poisoning a mild polycythaemia and leucocytosis. There have been no distinct changes observed in the blood pressure. Tremor was found only in 6 cases as objective neurological changes.

In short we may say that the CO-poisonings caused by motor gas have generally been very mild and approximately twice less common than in drivers of cars operated by charcoal gas.

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Aus der medizinischen Abteilung des städtischen Krankenhauses Kivela zu Helsinki. Damaliger Vorstand: Professor Dr. Arvo Vesa.

## Untersuchungen über die QT-Dauer im Elektrokardiogramm.<sup>1</sup>

Von

MARTTI SAVILAHTI.

(Bei der Redaktion am 2. Februar 1945 eingegangen).

Die Abhängigkeit der Systolendauer des Herzens von der Pulsfrequenz ist schon vor Einführung der elektrokardiographischen Untersuchungsmethode ein Forschungsgegenstand gewesen (Waller 1891). Lombard und Cope (1919) bestimmten aufgrund der von ihnen am Karotispuls gemessenen Werte eine Formel, an Hand welcher sich die Systolendauer aus der Länge der Pulsperiode bestimmen lässt. Die etwas modifizierte Formel hat folgendes Aussehen:  $S(ystole) = 0.319 \sqrt{P(eriode)}$ .

Die im Ekg gemessene QT-Dauer entspricht gemäss neuerer Untersuchungen am besten der totalen Systole, und so ist denn diese Frage in den letzten Jahrzehnten vorwiegend elektrokardiographisch untersucht worden. Bazett (1920) wandte die oben mitgeteilte Formel auf die QT-Dauer an und bemerkte, dass sie zutreffend war, jedoch mit dem Unterschied, dass der Koeffizient etwas grösser (bei Männern 0.37, bei Frauen 0.40) ausfiel, was darauf beruht, dass man am Karotispuls nur die Austreibungszeit

<sup>1</sup> (Diese Arbeit ist schon 1941 in extenso als akademische Abhandlung in der Publikationsserie der Acta Societatis Medicorum Fennicae »Duodecim« Ser. B. Tom. XXX, Fasc. 3 erschienen, aber dieses Referat ist infolge des Krieges verzögert worden. Aus demselben Grunde ist das später erschienene Schrifttum unberücksichtigt geblieben).

messen kann, während die QT-Dauer die ganze Systole wiedergibt. Diese Bazett'sche Formel ist auch jetzt noch allgemein im Gebrauch, insbesondere in den angelsächsischen Ländern. Um dieselbe Zeit leitete Fridericia für die QT-Dauer die Formel:  $S = 8.22 \sqrt[3]{P}$  ab, worin S und P in 0.01 Sek. ausgedrückt sind. Diese Formel ist bis in den letzten Jahren in den meisten europäischen Ländern in Gebrauch gewesen. Die erwähnten Formeln stellen Mittelwerte dar, von denen Q—T in Einzelfällen auch physiologisch etwas abweichen kann, nach Fridericia höchstens um 0.045 Sek. ( $= 3 \times$  der Mittelfehler).

Diese Ergebnisse sind mehrfach kontrolliert worden. Die umfangreichsten Materialien bringen Hegglin und Holzmann (1937) mit 700 Normalfällen sowie Hecht und Korth (1937) mit 1016 Fällen. Die ersteren halten die Formel von Lombard und Cope (Bazett) für geeignet. Der Koeffizient beträgt nach ihnen bei beiden Geschlechtern 0.39 und die grössten Abweichungen betragen 0.04 Sek. von dem berechneten Mittelwert. Die zuletzt erwähnten Autoren begnügen sich mit der Angabe der Grenzwerte, zwischen denen Q—T in dem jeweiligen Frequenzgebiet variiert. Aus Fig. 1 sind die von den verschiedenen Forschern erhaltenen Resultate ersichtlich. Die Formeln von Bazett und Fridericia weichen also erheblich voneinander ab, allerdings nicht in dem wichtigsten Frequenzgebiet; aber wenn es sich um die QT-Dauer bei höheren Frequenzen, wie besonders bei Kindern, Fiebernden und nach Belastung handelt, hängt es ganz davon ab, welche Formel wir gebrauchen, ob die festgestellten Werte als normal oder als pathologisch zu gelten haben.

Die QT-Dauer bei Kindern ist u. a. von Engel (1937), Nádrai (1938) sowie Ohr und Porsche (1940) untersucht worden. Die Formel von Fridericia hat sich hierbei als ungeeignet erwiesen, am besten passt die Formel von Hegglin und Holzmann, aber die physiologischen Abweichungen vom Mittelwert sind nicht so gross, wie diese Forscher angeben. Die aus dem Schrifttum erhaltenen Angaben darüber, ob Q—T in den verschiedenen Altersklassen schwankt, sind spärlich und widersprechend. Schlomka und Raab (1936) stellen fest, dass sich Q—T mit dem Alter ein wenig verlängert, aber ein deutlich wahrnehmbarer Unterschied erscheint erst bei Greisen. Dies könnte auf eine Verschlechterung des Koronarkreislaufs zurückzuführen sein, was, wie mehrere Forscher beobach-



tet haben, die QT-Zeit verlängert (Büchner, Weber und Haager 1935, Hegglin und Holzmann, Hegglin und Nobile 1939). Die Ergebnisse sind jedoch widersprechend, denn bei Tierversuchen hat man das Umgekehrte beobachtet (Miki 1922, Opitz 1936, Aschenbrenner 1937).

Nach Belastung haben mehrere Forscher eine abnorme Verkürzung in der QT-Dauer konstatiert (Fridericia, Herxheimer 1924, Schwingel 1937, Rihl, Huttman und Spiegl 1935, Schöne 1936 Schlomka und Reindell 1936). Als abnorm verkleinert hat man die Werte betrachtet, weil sie von den aus der Formel von Fridericia berechneten Mittelwerten abweichen, die, wie oben angeführt wurde, bei hohen Frequenzen zu gross sind. Ob in der QT-Dauer bei Gesunden und bei Koronarsklerotikern nach Belastung ähnliche Veränderungen stattfinden, oder ob bei den letzteren Veränderungen angetroffen werden, aus denen man Nutzen beim Stellen der Frühdiagnose von Koronarinsuffizienz ziehen könnte, ist im Schrifttum nicht klargelegt.

Eine im Zusammenhang mit akuten Infektionskrankheiten auftretende Myokarditis ist oft schwer diagnostizierbar. Auch der Ekg-Befund kann völlig normal sein. Der QT-Dauer ist sehr wenig Beachtung geschenkt worden. Man hat indessen bemerkt, dass ein abnorm langes Q—T das einzige pathologische Symptom sein kann. Wann Q—T bei einem Fiebernden abnorm lang ist, lässt sich jedoch schwer entscheiden, denn wir wissen nicht mit Sicherheit, wie lang die normale QT-Dauer bei der Fiebertachykardie ist. Die Sache ist recht wenig untersucht worden. Hegglin und Holzmann halten die bei Fieber gemessenen Werte ohne weiteres für normal und benutzen sie beim Berechnen ihrer Formel.

Aufgrund des oben Ausgeführten ergibt sich als Thema dieser Arbeit die Untersuchung der QT-Dauer besonders bei hoher Pulsfrequenz und zwar bei Kindern, bei Fieberzuständen sowie nach Belastung, getrennt bei jungen, gesunden Personen und bei solchen, die bereits das Koronarsklerosealter erreicht haben.

#### *Material und Untersuchungsmethode.*

Das Kindermaterial umfasst 227 Kinder aus der Universitäts-Kinderklinik zu Helsinki. Hiervon waren 165 hinsichtlich ihres Kreislaufsystems gesund, 55 hatten einen organischen Herzfehler und 7 Spasmophilie. Von den gesunden Kindern wurden insgesamt

300 und von den kranken 100 Ekg aufgenommen. Das Alter der Kinder schwankte zwischen 1 Woche und 15 Jahren. Der Einfluss des Fiebers wurde untersucht bei 38 an verschiedenartigen Infektionskrankheiten leidenden Patienten des Epidemiekrankenhauses von Helsinki, deren Herzstatus während der ganzen Krankheit genau beobachtet und bei denen auch gelegentlich der Nachuntersuchung nichts auf eine Myokarditis Hinweisendes bemerkt wurde. Die Untersuchungen gründen sich auf 50 während des Fiebers und ebensoviele in der fieberfreien Periode aufgenommene Ekg.

Die Untersuchungen nach Belastung und nach dem Aufstehen wurden bei 60 unter 45 Jahre alten Patienten des Kiveliä-Krankenhauses angestellt, die keine Anzeichen eines Herzfehlers darboten, sowie bei 50 über 45 Jahre alten, die zum grössten Teil Anzeichen eines verschlechterten Koronarkreislaufes aufwiesen, wenn auch keine klassischen Angina-pectoris-Anfälle und keine klinisch nachweisbaren Symptome von Herzinsuffizienz vorkamen. Im Ekg kam kein Schenkelblock vor. Das Ekg wurde in Ruhe beim Liegen, sowie 10, 30 und 60 Sek. nach dem Aufstehen aufgenommen. Danach liess man die zu Untersuchenden so lange rasch Treppen hinauf- und hinuntergehen, dass sich bei allen eine deutliche, ungefähr gleich starke Dyspnoe einstellte, wozu im allgemeinen 2—5 Stockwerke genügten. Hierauf wurde das Ekg nach 10 und 30 Sek. sowie nach 1, 2, 3, 5 und 10 Min. aufgenommen. Ausserdem wurden einige Sonderfälle untersucht.

Das ganze Material umfasst 227 Kinder und 156 Erwachsene, insgesamt 383 Personen, von denen 618 Ekg in Ruhe, 354 im Stehen und 840 nach Belastung, alles in allem 1812 Ekg, aufgenommen wurden.

Die QT-Dauer wurde bei den in Ruhe aufgenommenen Ekg in den drei Ableitungen gemessen und observiert dort, wo sie am längsten war. Wenn T deutlich wahrzunehmen war, bestanden keine augenfälligen Unterschiede in den verschiedenen Ableitungen. Wurden Unterschiede bemerkt, so war Q—T am längsten in der Ableitung, wo T am deutlichsten ausgeprägt war, gewöhnlich in der II. Nach der Belastung war es technisch unmöglich, mit dem verfügbaren transportablen Siemenschen Elektrokardiographen alle Ableitungen so rasch aufzunehmen. Aus diesem Grunde wurde das Ekg nur in der Ableitung aufgenommen, wo T am deutlichsten war. Die Pulsfrequenz wurde im allgemeinen aufgrund von 5

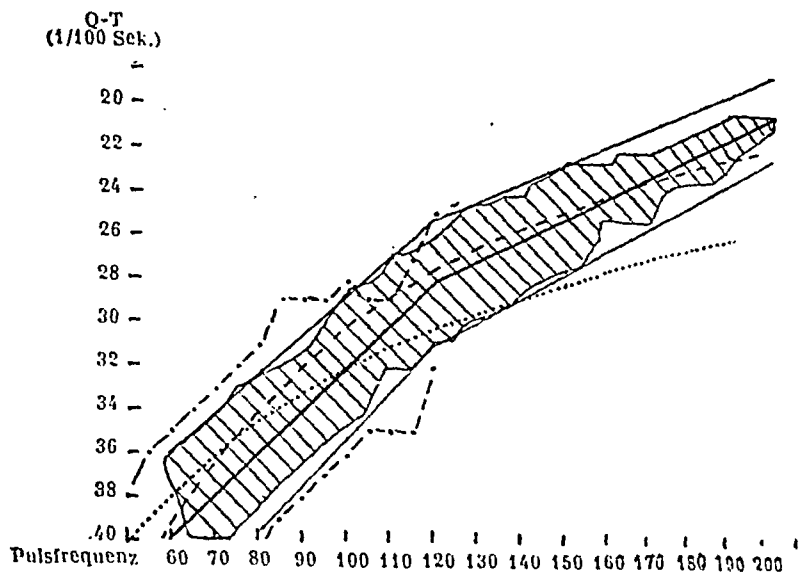


Fig. Nr. 1.

Auf das schraffierte Gebiet entfallen die bei gesunden Kindern gemessenen Werte der QT-Dauer.

— = Die nach den obigen bestimmte Mittelwertlinie sowie die um  $\pm 10\%$  davon abweichenden Werte.

..... = Fridericias Kurve.

----- = Bazetts (Hegglin-Holzmanns) Kurve.

..... = Grenzwerte nach Hecht und Korth.

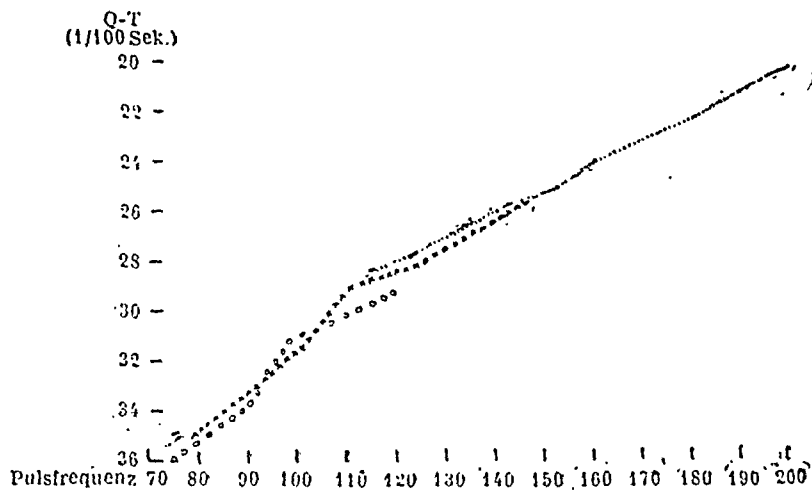


Fig. Nr. 2.

Kurven, welche die für Kinder verschieden Alters berechneten mittleren Längen der QT-Dauer wiedergeben.

..... = unter 1 Jahr,  $\times \times \times$  = 1—10 Jahr, oooo = 10—15 Jahre alte Kinder.

Schlägen berechnet, wenn aber eine Arrhythmie vorlag, wurden bis zu 10 Schlägen gemessen. Die Messung der QT-Dauer wurde, wie üblich, vom Anfang von Q (R) bis zum Ende von T ausgeführt.

### *Die QT-Dauer bei gesunden Kindern.*

Um einen eventuellen Einfluss des Alters herauszubringen, wurden die gesunden Kinder in 3 Altersgruppen, die unter 1 Jahr alten, die 1-10jährigen und die 10-15jährigen, eingeteilt. Zu der ersten Gruppe gehören 76 Kinder (200 Ekg), zu der zweiten 59 Kinder (66 Ekg) und zu der dritten 30 Kinder (34 Ekg). Aufgrund der Pulsfrequenz wurde das Material in verschiedene Gruppen eingeteilt, und in jeder Gruppe wurden die mittlere Frequenz und die QT-Dauer bestimmt. Bei der graphischen Darstellung erhält man die in Fig. 2 dargestellten Linien. Die Linien, welche die in den verschiedenen Altersklassen erhaltenen Mittelwerte wiedergeben, weichen also recht wenig voneinander ab und kreuzen einander sogar. Nach meinem Material zu schliessen *übt also das Alter bei Kindern keinen Einfluss auf die QT-Dauer aus.*

Bei höherer Frequenz verlaufen diese Linien sehr nahe an der Geraden, die durch die Punkte  $\text{Freq.} = 120, Q - T = 0.28$  und  $\text{Freq.} = 200, Q - T = 0.20$  gezogen ist, sodass diese Gerade die von mir bei Kindern erhaltenen Mittelwerte darstellt. Bei niedrigerer Frequenz kann schon ein Vergleich mit den entsprechenden Mittelwerten bei Erwachsenen in Frage kommen. Wie wir später sehen werden, entsprechen die von Hecht und Korth angegebenen Mittelwerte am besten den Resultaten des Verfassers, und ihr Untersuchungsmaterial ist am umfangreichsten. Aus diesem Grunde habe ich den Mittelwert der von ihnen mitgeteilten Grenzwerte als Masstab benutzt. Die Gerade, die von dem Punkt  $\text{Freq.} = 60, Q - T = 0.40$  nach dem Punkt  $\text{Freq.} = 120, Q - T = 0.28$  verläuft, zieht sehr genau in der Mitte zwischen den von ihnen aufgestellten Grenzwerten dahin. Von dieser Geraden weichen die von mir berechneten Mittelwerte höchstens um einige Tausendstel Sekunden ab, sodass also die *QT-Dauer bei Kindern und Erwachsenen, falls die Frequenz die gleiche ist, wenigstens praktisch betrachtet, gleich lang ist.* Die Differenzen sind jedenfalls kleiner als die bei der Messung vorkommenden Fehler.

In meinem Material sind von 147 Mädchen und von 153 Knaben Ekg aufgenommen worden. Die QT-Dauer bei Mädchen ist mit

Rücksicht auf die Frequenz durchschnittlich um 0.0016 Sek. (= 0.6 %) länger als bei Knaben. Der Unterschied ist also ganz belanglos und wahrscheinlich zufällig.

Die physiologischen Schwankungen sind bei hoher Frequenz bei weitem nicht so gröss, wie sie nach Fridericia sowie Hegglin und Holzmann sein dürfen. Es ist ja auch natürlich, dass, da der absolute Q—T-Wert hierbei niedriger ist, auch die Schwankungen in beiden Richtungen geringer sein müssen. Aufgrund meines Materials *weicht der Q—T-Wert in Einzelfällen um höchstens 10 % vom Mittelwert ab*. Dasselbe gilt, wie wir später sehen werden, auch für Erwachsene.

#### *Die QT-Dauer bei Kindern mit Herzkrankheiten und Spasmophilie.*

Das Material umfasst 35 Kinder, die an Endo-, Myo- oder Pankarditis litten (zus. 68 Ekg), 20 mit Klappenfehlern oder angeborenem Herzfehler (22 Ekg) und 7 mit Spasmophilie (10 Ekg).

Die Messungen erweisen, dass bei Klappenfehlern und angeborenen Herzfehlern keine sichere Abnormität in der QT-Dauer wahrzunehmen ist. Auch bei den Karditiden hielt sich Q—T grösstenteils innerhalb der angegebenen Grenzwerte. In 11 Fällen war sie jedoch um mehr als 10 % länger als der Mittelwert, in einem sogar um 20 %. In einigen Fällen war die abnorm lange QT-Dauer auch das einzige pathologische Zeichen im Ekg. *Der grösste Teil dieser Verlängerungen wäre beim Gebrauch der früher dargestellten Formeln und Grenzwerte innerhalb der normalen Grenzen geblieben*. Im Durchschnitt war Q—T bei den Karditiden um 0.01 Sek. länger als bei den Gesunden. Bei den spasmophilen Kindern war Q—T bei allen Messungen länger als der Mittelwert, 7mal überstieg die Abweichung die Grenze von 10 %.

#### *Die QT-Dauer bei Erwachsenen in Fieberzuständen.*

Während der Aufnahme des Ekg variierte das Fieber der Patienten zwischen 37.5 und 41°, die Pulsfrequenz zur gleichen Zeit zwischen 60 und 170, bei einem Mittelwert von 95½, bei denselben Patienten nach der Entfieberung 55—100, durchschnittlich 76½. Die Q—T-Werte verteilten sich sehr gleichmässig zu beiden Seiten der eben dargestellten Mittelwertlinie, von der sie höchstens um 0.026 Sek. abwichen. Nach dem Fieber wurde der Q—T-Wert bei denselben Patienten kontrolliert und hierbei festgestellt, dass der-

selbe bei allen Fällen nach wie vor zu beiden Seiten der Mittelwertlinie blieb und nur bei zweien um mehr als 0.02 Sek. davon abwich. Die mittlere Abweichung betrug — 0.003 Sek. Die Differenz in der QT-Dauer während des Fiebers und nach der Entfieberung war also verschwindend klein; man kann sagen, dass das *Fieber keine messbare Abnormität in der QT-Dauer verursacht*. Wenn wir eine solche feststellen, liegt Verdacht auf Myokarditis vor.

### *Die QT-Dauer in Ruhe und nach Belastung.*

Bei 60 gesunden unter 45 Jahre alten Versuchspersonen wurde zuerst Q—T in Ruhe gemessen. Die Frequenz schwankte zwischen 50 und 100. Die Q—T-Werte verteilten sich derart zu beiden Seiten der in Abb. 1 dargestellten Mittelwertlinie, dass Q—T bei 26 kürzer als der berechnete Mittelwert bei 3 genau ebenso gross und bei 31 länger war. Bei niedrigeren und höheren Frequenzen waren die Abweichungen in beiden Richtungen gleich gross und betrugen keinmal über 10 % des Mittelwertes.

Seitens ihrer Kreislauforgane gesunde Kinder und Fieberkranke ohne Herzkomplicationen haben aufgrund meiner Untersuchungsergebnisse eine ebenso lange QT-Dauer wie gesunde Erwachsene mit der gleichen Pulsfrequenz. Zur Gewinnung eines einheitlicheren und anschaulichen Bildes von der QT-Dauer in diesen Normalfällen habe ich die bei ihnen erzielten Messungsergebnisse in eine und dieselbe Figur (Nr. 3) eingetragen. Die die Mittelwerte darstellende Linie ist eine gebrochene Linie, und es ist offenbar, dass die Linie, welche die QT-Dauer wiedergibt, in der Tat eine Kurve ist. Dies ist auch aus der Figur ersichtlich, worin die gestrichelte Linie (----) den genauen arithmetischen Mittelwert darstellt. Ich habe bewusst die Bestimmung solcher Werte angestrebt, die leicht zu behalten und zu verwerten sind, wenn man die Abweichungen der QT-Dauer vom Mittelwert und die Grenzen berechnet, innerhalb welcher sich dieselbe normalerweise hält. Deswegen sind die Werte in geraden Zahlen bestimmt worden. Die nach der gebrochenen Linie bestimmten Werte weichen an keiner Stelle mehr als höchstens um einige Tausendstel Sekunden von den berechneten Mittelwerten ab, sodass die Abweichungen nur einen Bruchteil von dem wahrscheinlichen messungstechnischen Fehler bilden, also praktisch belanglos sind.

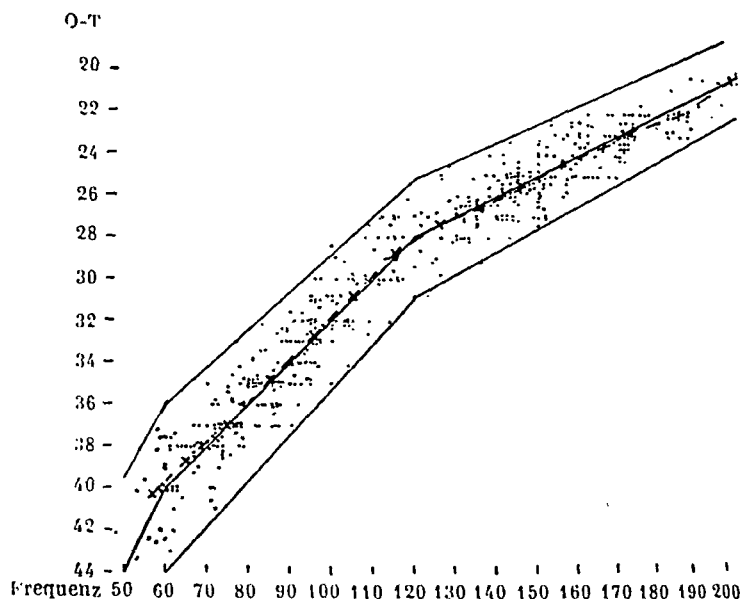


Fig. Nr. 3.

Messungsergebnisse bei gesunden Kindern und Erwachsenen in Ruhe.

----- = arithmetische Mittelwertkurve.

——— = die Linien, welche die in geraden Zahlen abgerundeten Mittelwerte und die um  $\pm 10\%$  davon abweichenden Werte darstellen.

Die Durchschnittswerte bei den verschiedenen Frequenzen sind für die QT-Dauer nach meinen Untersuchungen folgende:

Frequenz:	60	70	80	90	100	110	120	130	140	150	160	170	180	190	200
QT-Dauer:	40	38	36	34	32	30	28	27	26	25	24	23	22	21	20

(in 1/100 Sek.).

Den Durchschnittswert der QT-Dauer kann man auch durch folgende möglichst einfache Formeln ausdrücken: Wenn die Frequenz 60—120 ist,

$$Q-T = 52 - \frac{\text{Freq.}}{5} \text{ (in 0.01 Sek.)}$$

und wenn die Frequenz 120—200 ist,

$$Q-T = 40 - \frac{\text{Freq.}}{10}$$

Die grössten Abweichungen betragen höchstens 10 % von den angegebenen Werten. Alter, Geschlecht und Körpertemperatur verursachen keine messbaren Differenzen.

Bei einem Vergleich der von mir erhaltenen Resultate mit den

früher dargestellten Formeln bemerken wir deutliche und entscheidende Unterschiede. Die aus der Formel von Fridericia berechneten Werte sind bei niedrigen Frequenzen zu klein und bei hohen viel zu gross. Die Werte Bazetts sind bei hohen Frequenzen tauglich, aber bei den Frequenzen 70—100 deutlich zu klein. In mein Material gehen mehrere Fälle ein, die nach Hegglin und Holzmann pathologisch sein würden. Innerhalb des von Hecht und Korth untersuchten Frequenzgebietes fallen meine Resultate in der Mitte zwischen die von ihnen angegebenen Grenzwerte. So grosse Abweichungen vom Mittelwert wie diese Forscher habe ich indessen nicht angetroffen.

Nach Belastung haben die meisten Forscher eine abnorm verkürzte QT-Dauer gefunden. Wenn man, wie es allgemein geschehen ist, die Werte von Fridericia als Masstab benutzt, gilt dies auch in bezug auf meine Ergebnisse. Vor Belastung hatten 48 von 60 Untersuchten ein längeres Q—T als der Fridericiasche Wert, nach Belastung nur 3, also 57 ein kürzeres. Ein ganz anderes Resultat erhält man jedoch, wenn man die nach Belastung gemessenen Werte mit den eben von mir angeführten Normalwerten vergleicht. Die 10 Sek. nach Belastung festgestellten Q—T-Werte entsprechen im allgemeinen ungefähr genau der dann vorkommenden schnellen Frequenz. In einigen Fällen ist jedoch eine abnorme Verkürzung zu beobachten und zwar dann, wenn die Frequenz nur wenig beschleunigt ist. Die Verkürzung übersteigt auch dann nicht oft die als normal anzusprechende Grenze von 10 %. Durchschnittlich war Q—T um 0.009 Sek. kürzer als der berechnete Mittelwert. In 30 Sek. nach Arbeit aufgenommenen Ekg tritt die Verkürzung deutlicher in Erscheinung. Q—T ist nunmehr 0.018 Sek. zu kurz. Eine abnorme Verkürzung hatte bei denjenigen stattgefunden, bei denen die Pulsfrequenz rasch gesunken war. Q—T war der ein wenig früher aufgetretenen Frequenz entsprechend geblieben. Dieselbe Beobachtung konnte man noch in den 1 Min. nach der Arbeit aufgenommenen Ekg anstellen. Während der folgenden Minuten, begann der Puls sich bei vielen erneut zu beschleunigen, insbesondere bei solchen, bei denen er sich sehr rasch verlangsamt hatte. Auf diese sekundäre Frequenzbeschleunigung folgte keine entsprechende Verkürzung der QT-Dauer, und so wurden ja in derartigen Fällen an gewissen Zeitpunkten ein abnorm langes Q—T angetroffen.



Man kann sagen, dass die QT-Dauer nach der Belastung im allgemeinen der Frequenz entspricht; aber während der ersten Minuten findet man bei Personen, bei denen sich die Frequenz rasch verlangsamt hat, ein abnorm kurzes und während der nächstfolgenden Minuten wiederum bei einigen ein abnorm langes Q—T. Dies kommt bei solchen Personen vor, bei denen die Frequenz von neuem zugenommen hat. Hieraus geht hervor, dass die QT-Dauer, obwohl sie im allgemeinen von der Frequenz abhängig ist, doch raschen Schwankungen derselben nicht folgt. Die Erscheinung findet ihre Erklärung wahrscheinlich darin, dass der chronotrope Faktor beim Schwanken des Vagosympathikotonus— wie früher festgestellt worden ist — am empfindlichsten auf das Herz einwirkt. Derselben Erscheinung begegnen wir auch bei Betrachtung der im Zusammenhang mit der respiratorischen Arrhythmie und Stellungsänderungen auftretenden Veränderungen. Es ist also zu berücksichtigen, dass die Ursache einer abnorm verlängerten oder verkürzten QT-Dauer einfach in den im Untersuchungs Augenblick erfolgten raschen Frequenzschwankungen liegen kann, wie sie bei neurolabilen Patienten sogar sehr oft vorkommen. Die Veränderung ist natürlich dann belanglos.

Die mit 10 zu Untersuchenden angestellten Versuche erwiesen, dass die Grösse der Belastung keinen Einfluss auf die QT-Dauer ausübt, wenn man die Verschiedenheit der Frequenz in Betracht zieht. Reindell hat insbesondere bei erschöpfenden Belastungen, die ich bei meinen Versuchen nicht angewandt habe, Unterschiede wahrgenommen.

#### *Die QT-Dauer bei alten Personen in Ruhe und nach Belastung.*

Das Material wurde aus solchen Patienten ausgewählt, bei denen geringfügige subjektive stenokardische Beschwerden, hoher Blutdruck, Symptome einer Koronarinsuffizienz im Ekg oder hohes Alter ohne diese Symptome vorlagen. Das Alter der Untersuchten schwankte zwischen 45 und 75 Jahren, der Blutdruck zwischen 110 und 270 mm Hg, bei einem Mittelwert von 163 mm. In Ruhe war die QT-Dauer durchschnittlich um 0.011 Sek. länger als die normale aber nur in einem Fall wurde ein deutlich abnormer, also um mehr als 10 % abweichender Wert angetroffen. Auch nach den vorgenommenen statistischen Berechnungen ist die festgestellte Verlängerung zuverlässig. Bei der getrennten Untersuchung der QT-Dauer bei unter und über 60 Jahre alten Personen wurde

kein Unterschied konstatiert. Hierauf wurde das Material aufgrund des Blutdrucks in drei Gruppen eingeteilt und in jeder Gruppe getrennt die durchschnittliche Frequenz und QT-Dauer bestimmt. Unterschiede ergaben sich hierbei nicht. *Alter und Blutdruck übten also nach meinem Material keinen unmittelbaren Einfluss auf QT-Dauer aus.*

Die QRS-Zeit betrug bei den Untersuchten im Durchschnitt 0.09 Sek. bei den jungen Personen des Materials 0.084. Die Differenz war somit geringer als bei der QT-Dauer. Auch bei denjenigen, bei welchen die QT-Dauer unter 0.1 Sek. blieb, war dieselbe länger als bei den jungen Personen. Die Verlängerung von Q—T verteilte sich also auf die QRS-Zeit und das S-Ende T.

Die verlängerte QT-Dauer ist als eine Reaktion des geschädigten Myokards zu betrachten. Es kann sich um Myokarditis oder um eine chronische, von mangelhafter Nutrition des Muskels herührende Degeneration handeln, wie es in dem vorliegenden Material der Fall war. Auch eine akut entstandene Nekrose kann die QT-Dauer nachgewiesenermassen verlängern.

Die Veränderungen *nach Belastung* weichen minimal von den bei jungen Personen festgestellten ab. Die QT-Dauer blieb während des ganzen Versuches ebenso wie in Ruhe ca. 0.01 Sek. länger als im entsprechenden Versuchszeitpunkt bei jungen Personen. Sofern Unterschiede im Vergleich mit jungen Personen wahrzunehmen sind, unterscheiden sie sich eher in der Hinsicht, dass bei den Alten weniger abnorm verkürzte und abnorm verlängerte Q—T-Werte konstatiert werden, was offenbar darauf beruht, dass bei diesen keine so raschen Frequenzschwankungen vorkommen, im Zusammenhang mit welchen bei jungen Personen abnorme Veränderungen angetroffen wurden. Fig. 4 zeigt die Schwankungen der Pulsfrequenz und der QT-Dauer bei jungen und alten Personen nach der Belastung. Auf der Y-Achse ist bei der Frequenz die ihr entsprechende normale QT-Dauer vermerkt, sodass man aus dem gegenseitigen Verhältnis der diese darstellenden Kurven ersieht ob Q—T länger oder kürzer als der Normalwert ist.

Obleich der Koronarkreislauf in der letzteren Gruppe meines Materials nach der Belastung sicher viel schlechter als bei den Jungen wurde, war also in der QT-Dauer kein deutlicher Unterschied wahrzunehmen. Dies erweist, dass wenigstens ein solcher Anoxiegrad, wie er bei der gewöhnlichen Belastungsprobe erreicht

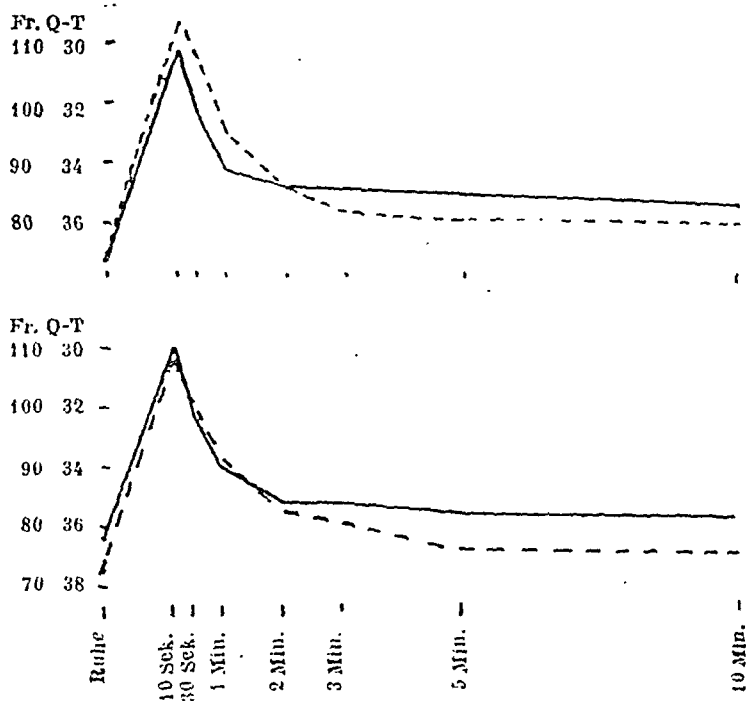


Fig. Nr. 4.

Schwankungen der Pulsfrequenz und der QT-Dauer zu verschiedenen Zeitpunkten nach Belastung; Mittelwerte der Messungsergebnisse.

— = Pulsfrequenz, ---- = QT-Dauer.

Oben die jungen, unten die über 45 Jahre alten Personen.

wird, nicht genügt, um abnorme Veränderungen in der QT-Dauer hervorzurufen. Bei einigen an schwerer Stenokardie leidenden Patienten wurde eine ähnliche Belastungsprobe angestellt, und obgleich bei manchen von ihnen ein schwerer Angina-pectoris-anfall während der Probe entstand, war Q—T auch dann von normaler Länge. Aufgrund des Obigen kann man sagen, dass man bei dem Bestreben, eine beginnende Koronarinsuffizienz zu diagnostizieren, von der Messung der QT-Dauer keine Hilfe hat, unabhängig davon ob das Ekg in Ruhe oder nach Belastung aufgenommen worden ist.

### Q—T und die respiratorische Arrhythmie.

Bei den Kindern meines Materials war schon in Ruhe und bei jungen Erwachsenen nach Belastung oft eine respiratorische Arrhythmie zu konstatieren. Bei 40 Kindern war diese so ausgeprägt, dass

zwischen der kürzesten und längsten Periode ein Unterschied von über 0.1 Sek. bestand. Bei 22 von 60 Erwachsenen trat eine solche während der ersten zwei Minuten nach der Arbeit auf. Wenn die QT-Dauer bei diesen in üblicher Weise gemessen wird, stellt man fest, dass sie fast ausnahmslos bei allen kürzer als normal ist. Selbst bei oft auftretenden grossen Schwankungen der Periode bleibt Q—T meistens die ganze Zeit unverändert. Bisweilen wird es jedoch während des Expiriums 0.01 Sek. länger. Die von Schlomka und Hausen wahrgenommene paradoxe Verlängerung von Q—T während des Inspiriums habe ich kein einziges Mal beobachtet. *Die QT-Dauer entspricht sehr genau der schnellen Frequenz während des Inspiriums; durch die expiratorische Bradykardie wird sie nicht verlängert, sondern Q—T kann während des Expiriums sogar um 30 % abnorm verkürzt sein.*

Auch dieser Umstand erweist meines Erachtens, dass die Veränderungen in der QT-Dauer sich langsamer als diejenigen in der Frequenz vollziehen, wie man beim Betrachten der Veränderungen im Anschluss an Belastung bemerkt. Q—T passt sich der schnellsten Frequenz entsprechend an, damit die Diastole auch während des Inspiriums genügend lang bleibt und die Füllung des Herzens nicht erschwert wird.

### *Die QT-Dauer beim Stehen.*

Die Anpassung des Kreislaufsystems an die Veränderungen der Körperstellung verlangt ein grosses Funktionsvermögen desselben. Das Verhalten der QT-Dauer zu den Frequenzschwankungen ist relativ wenig untersucht worden, und die Ergebnisse sind widersprechend. Nach Schlomka und Reindell findet man gleich nach dem Aufstehen eine bedeutende Verlängerung von Q—T, welcher die Autoren bei der Beurteilung des Funktionsvermögens des Herzens grossen Wert beimessen. Nach Janzen (1938) kommt ihr jedoch keine Bedeutung zu.

Bei den jungen Personen meines Materials beschleunigte sich der Puls durchschnittlich von 74 auf 95  $\frac{1}{2}$ . Q—T verkürzte sich in derselben Zeit nur sehr wenig, bei manchen gar nicht, sodass es 10 Sek. nach dem Aufstehen ca 10 % zu lang war. Schon 20 Sek. später war der Puls im allgemeinen erheblich verlangsamt, aber Q—T entweder unverändert oder noch öfter ein wenig verkürzt.

sodass sie ziemlich genau der Frequenz entsprach. Eine halbe Minute später war der Zustand wie zuvor.

Bei Koronarsklerotikern verkürzte sich Q—T gleich nach dem Aufstehen um annähernd ebenso viel wie bei den jungen Personen, aber die Pulsbeschleunigung war im allgemeinen geringer, sodass die abnorme Verlängerung bei den erwähnten Patienten weniger deutlich hervortrat. Während der folgende Minute blieb die Frequenz im allgemeinen unverändert, Q—T verkürzte sich ein wenig.

In beiden Gruppen war also die QT-Dauer gleich nach dem Aufstehen abnorm lang, aber bei vielen herzgesunden jungen Personen war die Abweichung vom Normalen grösser als bei den Koronarsklerotikern. Q—T passte sich jedoch der Frequenz schon nach Verlauf von einer halben Minute an, sodass das Stehen an sich keine Änderung verursacht. Meines Erachtens handelt es sich auch hierbei um eine verspätete Anpassung der QT-Dauer. Beim Beurteilen der Funktionsfähigkeit des Herzens kommt dieser Erscheinung meines Erachtens keine Bedeutung zu.

## Summary.

### *Studies on the QT duration of the electrocardiogram.*

The material of the author consists of 383 persons, of whom altogether 1812 electrocardiograms have been taken. Of the examined persons 227 were children, of whom 165 were healthy, 55 were suffering from organic heart disease and 7 from spasmophilia. An electrocardiogram was taken of 60 soundhearted test patients under 45 years of age at rest, 10, 30 and 60 sec. after standing up and of the same persons after 10 and 30 seconds and also 1, 2, 3, 5 and 10 minutes after exercise, which caused a distinct shortness of breath. A similar test was made to 50 persons over 45 years of age, of whom a large part had high blood pressure, mild stenocardiac pains or small changes in electrocardiogram due to coronary sclerosis.

According to the author, children of all ages and adults under 45 years of age have the same QT time provided that the frequency is the same. The QT time varies according to the frequency as follows:

Frequency:	60	70	80	90	100	110	120	130	140	150	160	170	180	190	200
QT time:	40	38	36	34	32	30	28	27	26	25	24	23	22	21	20

The same thing can be expressed by following simplest possible formulae: If the frequency is below 120,  $QT = 52 - \frac{\text{frequency}}{5}$ , if

the frequency is over 120,  $QT = 40 - \frac{\text{frequency}}{10}$ . The individual

cases differ at most 10 per cent from the average. There is no distinct difference between the sexes. The fever does not cause any obvious changes.

After the exercise young persons had usually as long a QT time as at the corresponding frequency at rest. If the pulse rate suddenly fell, an abnormal relative shortening of the QT time could be observed after such a fall. If the rate during following minutes increased anew, as it often did, the QT time remained abnormally long.

The abnormal changes were most distinct in persons, who had respiratory arrhythmia. In this case the QT time corresponds to the inspiratory rapid frequency. The same thing was observed in children.

If the rate after standing up suddenly increased, a distinct relative prolongment was observed in the QT time, which prolongment disappeared during following  $\frac{1}{2}$  minute. The above mentioned abnormal changes in the QT time may be due to the fact, that the changes in it occur 10—30 seconds later than in frequency.

The QT time of the old persons of the material was at rest approximately 0.01 sec. longer than the QT time of the young persons. The changes after exercises and standing up did not essentially differ from the changes found in young persons. Although these persons had relatively much worse coronary circulation than the young persons, at least this amount of anoxia attained in a regular exercise test did not cause any abnormal changes in the QT time.

The examinations of ill children show, that the QT time in most of the patients suffering from spasmophilia and in a part of the patients suffering from myocarditis was abnormally long, the increase exceeding the above-mentioned normal range of variation of 10 per cent. So this range seems to suit the clinical use. According to previously presented formulae, not very many of the cases could have been considered pathological.

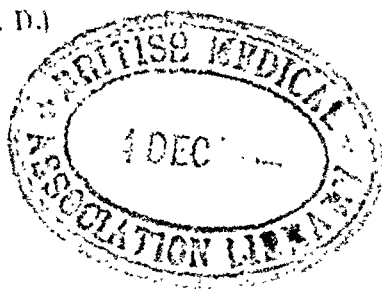
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From the First Medical Department, Sahlgren's Hospital, Gothenburg,  
Sweden.

(Acting Head: Dr. Bo Ewert, M. D.)



## Intermittent claudication and vascular spasm.

II. Can intermittent claudication be due to vascular spasm without accompanying structural disease of the arteries?

By

TORSTEN LINDQVIST, M. D.

(Submitted for publication March 15, 1945).

Many of the authors who have adopted the theory that vascular spasm is a genetic factor in intermittent claudication consider it quite possible that the syndrome may also occur in persons with no structural changes in the arteries.

This belief was first advanced in the form of a theory by Oppenheim (1), although he was unable to base his opinion on any definitely established facts. Cases of intermittent claudication where the symptoms were interpreted as being due to arterial spasm without concurrent structural disease were later reported by Westphal (2), Curschmann (3, 4), and Oppenheim (5). Since then, the existence of this «purely angiospastic form» has been largely acknowledged by the writers of the German textbooks. [Cf. Cassirer and Hirschfeldt, (6).] However, as far as I can find, there have been no new cases described in the European literature since the time of these publications. In the United States, Pearl (7) has reported on 6 cases in which he believed the intermittent claudication to be due solely to arterial spasm, and he came to the con-



clusion that »angiospastic claudication may occur in patients who have no organic arterial disease». If the purely angiospastic form were a common condition, as Curschmann (8) believes it to be, it would probably have aroused more interest. Leriche (9) denies its existence. He says: »La claudication intermittente ne se voit que chez les artéritiques».

In what measure, then, can we regard the above-mentioned observations as conclusive? There is no doubt but that, in the cases reported, the patients displayed the syndrome of intermittent claudication. If it were proved that the vessels were normal there could be no other way of explaining the symptoms than to assume that the blood supply was impaired only owing to arterial spasm. At the time when the earlier of these observations were made, however, there were few possibilities for diagnosing structural disease of the arteries with certainty. The fact that, in some patients, the pulse is some times distinguishable, sometimes absent, is no proof that the arteries are normal, since a palpable pulse is sometimes present even when the patient has severe arterial disease [Ratschow (10)]. And the absence of signs of calcification on an ordinary radiogram of the legs does not prove that there is no arteriosclerosis. Some authors quote as a proof that a simple spasm was in question the fact that the pains disappeared again after a time. This is not conclusive evidence, seeing that, as is generally known, the condition sometimes recedes again in certain patients with intermittent claudication due to advanced arterial disease. This fact is stressed by Oppenheim (5), for example, in his paper describing his two »proved» cases of the purely spasmodic form. Pearl advanced as a proof that his patients were not suffering from organic arterial disease the fact that they all showed a normal vasodilatation response after posterior tibial nerve block. This feature alone cannot be regarded as sufficiently conclusive evidence, however. Morton and Scott (11) have described 6 patients with intermittent claudication who all had a normal vasodilatation level when examined by this method but who all had obvious signs of structural disease of the arteries. One of Pearl's own cases had »slight calcification of the foot vessels on the right, moderate on the left». Arteriographic and oscillometric examinations were not carried out in his cases. It must be said regarding some of the cases reported as being examples of the spasmodic form of intermittent claudication that

it is hardly likely that they could have been free from structural disease of the arteries, and with regard to others, that the arguments advanced to support the theory that there was no arterial disease are inadequate.

Concerning the features cited as a proof of arterial spasm in these cases, the reader is referred to the criticisms which I have already advanced in a previous publication [Lindqvist, (12)].

In my own investigations on cases of intermittent limping, I have proved that in patients with structural changes in the arteries a noticeable decrease in the blood flow to the muscles of the calf can occur in the working limb. This can also occur in patients with only a slight degree of arterial obstruction. (Cf. case 8 in the above-mentioned publication.) This finding gives rise once again to the question of whether an arterial spasm might not also cause intermittent claudication in patients in whom arterial changes are wholly absent.

For the past nine months I have had under observation a patient in whom, beyond all doubt, there appears during exercise a definite reduction in the pulsations in both legs but in whom no disease of the arteries has been discovered.

### Report of a case.

B. B., a seaman aged 39 years. Record no. 1130/44.

He had previously always been healthy, apart from the fact that he had spent two periods in hospital on account of stomach trouble yielding no objective signs. He denied the possibility of venereal infection and had not used alcohol immoderately. For many years he had smoked about twenty cigarettes a day but he had recently reduced his consumption to about ten a day.

In October 1943 he noticed that after walking fast he had pains in the right foot, calf, and thigh, and that his leg felt numb. This discomfort soon subsided when he stopped walking. During the succeeding six months the pains grew worse, until at the beginning of May 1944, he could only walk 500—600 metres at an ordinary pace before experiencing the pains; if he walked fast the pains appeared after 50—100 metres. Ten minutes now often elapsed, after he stopped walking, before the pains disappeared. Some time after this, similar pains, though in a milder form, began to be experienced in the left leg also.

Because of these symptoms he was hospitalized on May 5, 1944 in the First Medical Clinic of Sahlgren's Hospital, and has since then been

admitted there on several different occasions. Between these periods in hospital, as well as subsequently, I have had him under observation as an ambulatory patient.

He is a thin man of rather frail build. The routine physical and neurologic examinations yielded nothing of interest. The blood pressure was 145/85. He was flat-footed in both feet. The Wassermann and other reactions in the blood serum were negative. The basal metabolic rate was plus 19 per cent.

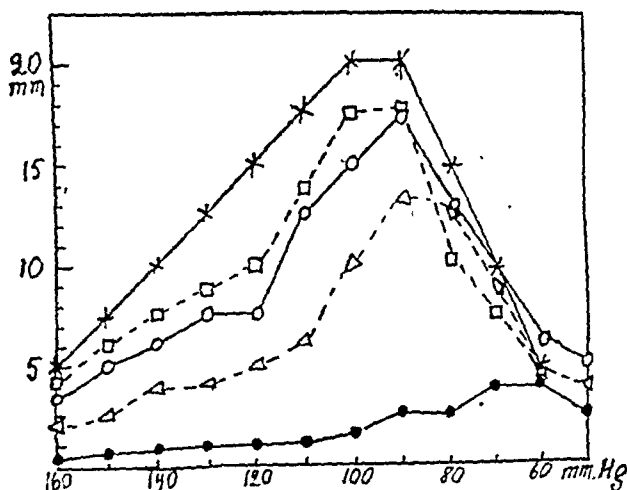


Fig. 1. Oscillometer values from the right calf.

—x—x—x—	Oscillations before work.
—•—•—•—	1—2 min. after work.
—△—△—△—	5—6 " " "
—○—○—○—	8—9 " " "
—□—□—□—	11—12 " " "

The pulse was readily palpated in both legs, both in the thigh and the popliteal fossa, behind the medial malleolus and on the dorsum of the foot, up to September 1944. After that it became more and more difficult to distinguish the pulses by palpation, and since December 1944 it has usually only been possible to palpate the pulse in the left groin.

*Oscillometric examination.* — All the tests were carried out with the apparatus devised by von Recklinghausen. This does not diverge in any essential details from Pachon's well-known apparatus, but it is easier to handle.

Tracings taken with the cuff placed round the thickest part of the left calf were as a rule 20—25 mm in size during the summer of 1944. On the right side, the tracings were somewhat smaller, but in most instances they went as high as 17—20 mm. If he walked 20—30 metres, the tracings were

usually a little larger than they were when he had been lying still for some time.

On the other hand, if the oscillometric examination was carried out after he had walked so far and so fast that he was experiencing severe pain, the results were entirely different. Figure 1 shows the tracings obtained after one of these examinations, which was made on June 14, 1944. Before the walk, the highest tracings from the right calf were 20 mm. After he had walked for 15 minutes on a hilly road the largest tracings measured only 4

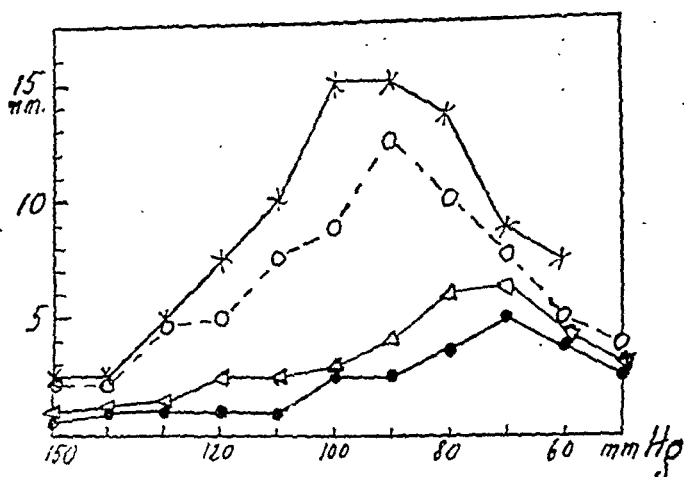
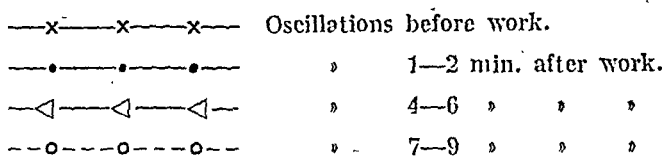


Fig. 2. Oscillometer values from the right calf after novocaine block of the right lumbar sympathetic chain.



mm. The decrease in the tracings was more noticeable with the higher pressures than with the lower. Within a period of about 15 minutes the pulsations gradually returned to their original size. The results were essentially the same in many different tests carried out on various occasions. Similar results to those obtained from the right calf have also been obtained from the left calf and from the thighs. While he has been under observation, however, the pulsations in the working limbs have on the whole become gradually smaller, and it is taking a longer and longer time for the pulsations to return to their initial values. Furthermore, during the observation time, the pulsations in the resting limbs have also tended to decrease. In January 1945, for instance, oscillations in the calf were often only 8—10 mm after the patient had been resting for several hours. They were sometimes stronger over the right calf than over the left, sometimes vice versa, and they showed many divergences from examination to

examination without there being any outward signs to account for these variations.

On June 13, 1944, an oscillometric examination was carried out on the resting and working limbs directly after the lumbar portion of the sympathetic chain on the right side had been infiltrated with novocaine solution (Dr. E. Moberg). That this intervention had had the desired effect was proved by the fact that the temperature in the toes of the *right foot* rose to 32—33° C. within 20 minutes of the injection. The results of the oscillometric tests are shown in figure 2. It will be observed that there was a noticeable decrease in the pulsations in the right calf after exercise, and that only after some time had passed were the pulsations back at their former level. The exercise was the same as that performed in the experiment shown in figure 1.

#### *Measurement of the skin temperature in the toes.*

a) *After blocking of the sympathetic chain in the lumbar region.* As I have just mentioned, this intervention resulted in a rapid rise in the skin temperature in the toes on the same side. On the other side, there was only a slight rise in the temperature during the same space of time. A Tykos »Dermatherm» (a copper-constantan element) was used for the measurements of the skin temperature.

b) *After spinal anaesthesia.* On Aug. 10, 1944, spinal anaesthesia was produced, the loss of sensibility being complete in both legs. As a result of this measure, the temperature in the toes rose to values of between 33.5° and 35.7° C, no difference being observed between the right and the left side. This experiment was repeated on Feb. 3, 1945, at a time when the peripheral pulsations in the legs were indistinguishable. The result was the same as before.

c) *With a body temperature raised through immersion in a hot bath.* For the past four years I have been carrying out this experiment in the following manner. The patient first sits for ten minutes with his feet in water having a temperature of 15° C. After his feet have been removed from the water and dried, measurements of the skin temperature in the toes are taken for a few minutes by means of a Tykos Dermatherm. After that, the patient is made to sit crosswise in a bath tub filled with water having a temperature of 43° C, his trunk and thighs being immersed in the water while his lower legs and feet are outside the tub. The measurements of the skin temperature in the toes are then continued. Figure 3 presents the results of an experiment of this kind carried out on May 31, 1944. The temperature in all the toes rose rapidly when once the rise had fairly started. The values obtained from the toes in which the rise was most rapid as well as those from the toe showing the slowest increase in temperature have been included in the figure. The other toes all showed practically the same rapid rate of increase as the first-mentioned toes; only the right big toe lagged behind a little. The temperature in the patient's rectum had risen to 40.1° C by the close of the experiment. The room temperature was 22° C during

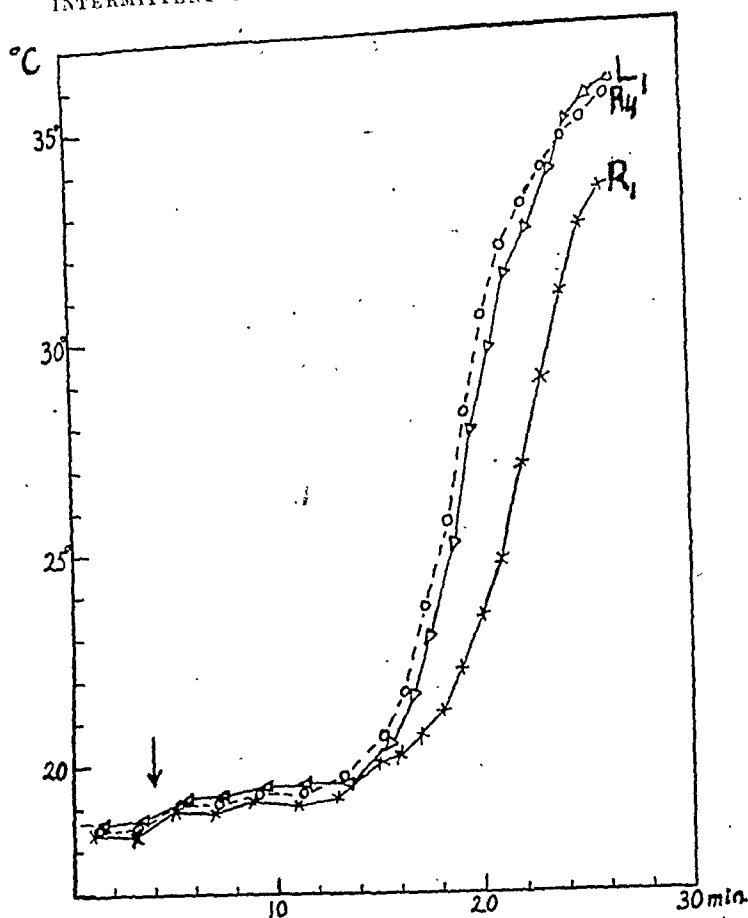


Fig. 3. Temperature of the toes with rising body temperature.

L<sub>1</sub> temperature of the 1st left toe  
 R<sub>1</sub> " " " " right toe  
 R<sub>4</sub> " " " " 4th " "

↓ immersion of the body into the hot bath.

the examination. (As a rule, during these experiments, I try to keep the room temperature at 15°C in order to be able to compare different curves with one another, but in this instance, owing to the time of year, it was not possible to achieve such a low temperature. However, as regards the essential features of the curves, the room temperature is of no consequence for the final assessment.) The same experiment was carried out on Jan. 12, 1945. Once again a rise in the temperature of the toes was obtained which must be described as fully normal both as regards the final temperature and the appearance of the temperature curve during the rise.

*Arteriographic examination.* On July 26, a percutaneous arteriographic examination of the vessels of the right leg was attempted, but unfortunately, the injection fluid flowed out around the artery. The attempt was repeated on Aug. 10, and this time the femoral artery was exposed. The

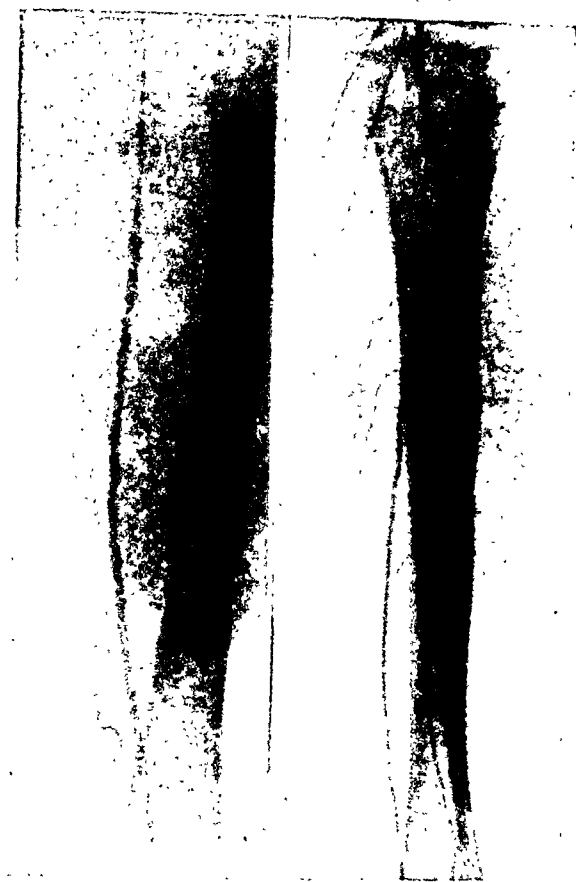


Fig. 4. Arteriograms of the left leg with 35 % perabrodil.

intervention was carried out under spinal anaesthesia which was made so complete that both legs were totally insensible. The contrast medium used was 35 per cent perabrodil solution. The radiograms showed normal filling of both the femoral artery and the arteries of the lower leg.

On Feb. 3, 1945 an arteriographic examination of the left leg was carried out after exposure of the femoral artery on the left side. As will be seen from the illustrations, the vessels are normal (see figs. 4 a and 4 b).

### Discussion.

a) *Is this a case of intermittent claudication of the purely angio-spastic type?* Oscillometric examination of the working limbs revealed that during exercise there was a strong decrease in the size of

the pulsations both in the thighs and in the calves. It seems to me that arterial spasm can be the only explanation of this reduction in the pulsations.

If this assumption is correct, the question then arises whether the spasm in this case was caused or facilitated by structural changes in the arteries or whether it was merely a matter of a spasm in vessels that were otherwise normal?

Judging from the literature and from my own experience, the oscillations obtained during the first period of observation were within the normal range. [Cf. Ratschow, (10); Philippides, (13).] They were closer to the lower borderline value than to the upper, however. Similar values can be observed also in patients with proved arterial changes. Reasoning from the size of the oscillations, therefore, it could be said that the vessels might very well have been normal, but not that they actually were so. The decrease in the oscillations in the resting limbs during the observation period caused me strongly to suspect that structural disease of the arteries was developing.

The arteriographic examination of the vessels of the thigh and lower leg revealed no pathologic features. At first sight, this would seem to indicate that the blood flow was normal, but it is not absolutely certain that such was the case. As a matter of fact, it is quite possible, under certain circumstances, for the flow of blood in the legs to be defective despite the fact that the vessels are normal. This is the case, for instance, in stenosis of the isthmus aortae. [See Lewis, (14).] I myself have encountered a patient with very severe intermittent claudication in both legs and ulcers on one foot who yielded absolutely normal arteriograms from the vessels of the leg. In this case there was in all probability some obstruction in the aorta. Very small pulsations were also obtained by oscillometry, and these are likewise the common finding in patients with stenosis of the isthmus aortae. Thus, taking into consideration the good pulsations in his legs, during the earlier part of the observation period, when he was resting, it is highly improbable that there could have been at that time any obstruction to the circulation in the aorta in the patient under discussion in this paper. Nor does it seem likely that the small pulsations occurring towards the end of the observation period, when the patient was at rest, could have been due to the fact that some abnormal process of



sufficient severity to cause such a powerful disturbance in the flow of blood to the legs had developed in the aorta.

When measurements of the skin temperature in the toes were taken after spinal anaesthesia, temperatures of between 33° and 35° C. were obtained in this patient. This finding has often been cited as a proof of the fact that in cases of this kind there can be no question of structural changes, but only of a purely spasmodic condition. [Cf. Gask and Ross, (15); Ratschow, (10); Homans, (16).] But this is no more a rule without exceptions than the matter of the arteriographic findings. I have observed a case where, after spinal anaesthesia, the above-mentioned temperature elevation was observed but where arteriographic examination disclosed the presence of a calcified thrombus which was wholly occluding the femoral artery in the middle of the thigh. In this case also oscillographic examination yielded tracings showing greatly decreased pulsations in the calf, and measurement of the skin temperature in the toes, with a raised body temperature by the method already described in this paper, revealed a much delayed temperature elevation in the affected leg as compared with that in the sound one, although the rise finally stabilized itself at the same value for both legs. It seems to me, therefore, that the last-mentioned type of examination is superior to that by which the rise in the skin temperature is measured after spinal anaesthesia, since with my technique it is not only the end result but the form of the rise also that can be determined.

However, as the measurements of the skin temperature in the toes, both after blocking of the lumbar sympathetic nerves and after spinal anaesthesia, as well as after raising of the body temperature, yielded absolutely normal values, a fact which can be interpreted as a proof of an exceedingly good blood flow when the vessels were dilated to their maximum extent, it must be said that it is very unlikely that obstructive arterial disease causing impairment of the blood supply could have been present.

Thus, the results of the different examinations taken separately provide no conclusive proof of freedom from structural changes in the arteries, but the combined result of all these investigations carries considerable weight as evidence to this effect. With our present diagnostic aids, this is about as far as we can expect to come in an attempt to rule out possible structural changes in the arteries.

There is still the possibility, however, that disease of the arterial walls without obstruction of the vascular lumen may have been present.

b) *The value of oscillometry after exercise.* The patient described in this paper, who was complaining of pains from intermittent claudication, yielded no pathologic features when he first presented himself even though he was submitted to exhaustive examination. Oscillometric examinations on the resting limbs, arteriography, and measurements of the skin temperature under varying circumstances furnished nothing to indicate the presence of arterial disease which might have served as the explanation of his pains. It seemed almost as though the condition was merely an aggravation of his flat-foot discomfort.

It was only when oscillometry was applied in connection with exercise that an objective sign to account for the severe pains could be discovered. During exercise, there was such a strong decrease in the pulsations that the necessary consequence was a high degree of ischemia in the working muscles.

This method of examination must therefore constitute a diagnostic aid of the utmost value in certain cases of intermittent claudication. It is mentioned in the French textbooks [see Parisot and Cornil, (17)], but it is overlooked in such exhaustive monographs as those by Gask and Ross (15), Lewis (14), Sunder-Plassmann (18), Ratschow (10), and White and Smithwick (19). If I had confined myself to the examination methods recommended in these monographs the diagnosis in the present case would undoubtedly have failed to be made, during the earlier part of the observation period, at least.

In this patient, there was a striking elevation in the skin temperature in the toes after blocking of the lumbar sympathetic chain as well as after spinal anaesthesia. Statements are often found in the literature to the effect that in cases showing these features there is a good chance that the pains will partly subside after lumbar sympathectomy. [Besides the monographs mentioned above, the reader is also referred to Rieder, (20).] In the present case, however, there was a strong arterial spasm during exercise, despite successful blocking of the lumbar part of the sympathetic chain. It would seem advisable, therefore, in patients with intermittent claudication upon whom the performance of a sympathectomy

is contemplated, to examine the limbs by oscillometry in connection with exercise after blocking of the lumbar sympathetic nerves also. It is possible that by doing so, a more suitable selection of patients for operation would be obtained.

### Summary.

There are mentioned in the literature a few cases of intermittent claudication where the symptoms are interpreted as being due to simple arterial spasm without concurrent structural disease of the arteries. The cases are not particularly convincing and the idea that intermittent claudication may be caused by arterial spasm alone does not seem to have won general acceptance.

The author describes a case, that of a man aged 39, in which there was the typical picture of intermittent claudication in both legs, most pronounced on the right side. By oscillometry, it was found that the pulsations in the lower legs and the thighs diminished considerably when the patient walked, while when he was at rest the oscillations were all within the normal range. Arteriographic examination revealed that the vessels in the thighs and lower legs were normal. Measurements of the skin temperature in the toes after spinal anaesthesia, after blocking of the sympathetic chain in the lumbar region, and with a raised body temperature, yielded normal findings. The sum of all these examinations would seem to indicate that there were no structural changes in the arteries. The author stresses the importance of using oscillometry both on resting and working limbs.

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From the Pathological Department of the Copenhagen County Hospital, Gentofte (Chief Pathologist: A. Sæborg-Ohlson, M. D.) and the Biological Department of Lovens kemiske Fabrik, Copenhagen.

## Methylthiouracil therapy in thyrotoxicosis.<sup>1</sup>

### Preliminary Report II.

By

JOHANNES THYSSEN.

(Submitted for publication February 22, 1945).

In a preceding paper the writer has dealt with thiouracil, especially the literature available on this subject, the mechanism of the action of the substance, and its clinical employment in thyrotoxicosis. In the same paper it was emphasized that, in comparison with thiouracil, thiourea has to be considered unsuitable as a therapeutic in cases of this kind.

Experimental studies carried out in the Biological Department of Lovens kemiske Fabrik, have given the result that *methylthiouracil* in rats has a strumogenic effect distinctly greater than that of thiouracil; the two remedies differ in toxicity but slightly. It seemed obvious therefore to try the therapeutic employment of methylthiouracil in thyrotoxicosis.

Before presenting the clinical experiences with this substance it is to be mentioned that also another derivative of thiouracil

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<sup>1</sup> Read before a staff-meeting in the Copenhagen County Hospital on November 27, 1944.

I wish here to acknowledge my indebtedness to the chiefs of the medical and surgical departments of the Copenhagen County Hospital Gentofte — Professor Poul Morville, Dr. E. Rosling, Dr. M. Siggaard Andersen, Dr. O. Kapel, Dr. F. Wulff, and Dr. H. Wulff — for their permission to treat patients admitted to their departments and for unbiased view concerning this treatment.

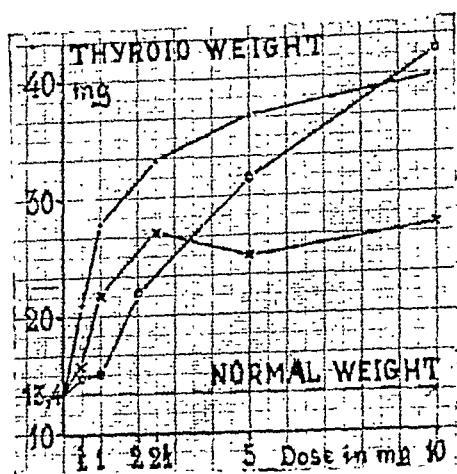


Fig. 1. Female rats, 6 months old, treated for 15 days with *thiouracil* (x---x), *methylthiouracil* (·-·-·) and *phenylthiouracil* (o---o).

— namely, *phenylthiouracil* (2-thio-6-oxy-4-phenylpyrimidin) — was found to have a quite considerable strumogenic effect in rats. In Fig. 1 this effect is compared graphically with that of *thiouracil* and *methylthiouracil*. When given in small doses, the strumogenic effect of *phenylthiouracil* appears to be essentially smaller than that of the other two substances mentioned, whereas it seems to exceed both of them in potency when the dose is increased a little. As, furthermore, the toxicity of this substance is lower than that of *methylthiouracil* as well as *thiouracil* (in rat experiments), we hoped here to have found a substance that would prove quite particularly serviceable in thyrotoxicosis. An experiment with its clinical employment, however, did not give the result expected (see Fig. 2). The patient was a woman, aged 47, with a moderate degree of exophthalmic goiter; and she was treated with 0.6 g *phenylthiouracil* daily for nearly 6 weeks. Under this treatment the thyrotoxic symptoms subsided somewhat, but the general condition of the patient was far from satisfactory, and the metabolism remained rather unchanged. When now *phenylthiouracil* was replaced by *methylthiouracil*, a very satisfactory result was soon obtained.

Since April 1944, in the Copenhagen County Hospital, we have tried out the therapeutic employment of *methylthiouracil* in thyrotoxicosis, and the aim of this paper is to present the clinical experiences we have gained in this way.

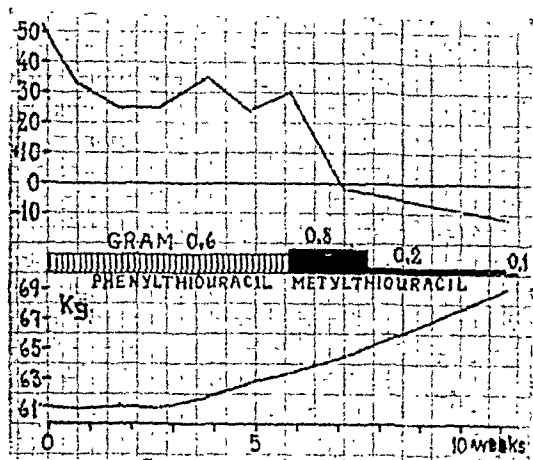


Fig. 2. Weight and metabolism curves for a female patient, aged 47, with moderate exophthalmic goiter, treated first with phenylthiouracil, then with methylthiouracil.

In the literature accessible to me, so far no report has been published from other countries on the effect of methylthiouracil in thyrotoxicosis. In this country, on the other hand, also other authors have observed the considerable strumogenic effect of this substance and tried to employ it clinically. Freiesleben, Kjerulf-Jensen, Meulengracht & Schmith (1) and Jersild & Nissen (2) thus have reported the therapeutic results obtained by them in 6 and 4 patients respectively; they found the substance to have a decided effect on the thyrotoxic condition of the patients.

Here no particular mention will be made of the biological experiments with methylthiouracil, as a few aspects of this question have been touched upon briefly in a preceding paper (4), and a subsequent work will give a thorough account of these experimental studies.

### Clinical Material.

Since April 1944, in the medical and surgical departments of the Copenhagen County Hospital we have treated altogether 28 thyrotoxicosis patients with methylthiouracil.

Of these 28 patients 20 were suffering from exophthalmic goiter (including one instance of recurrence after subtotal thyroidectomy; 3 had a thyrotoxic adenoma; and 1 had hyperthyroidism after taking thyroid preparations through many years.

Of the 28 patients 24 were women, aged from 21 to 69 years, 4 men, from 40 to 51 years old.

Operative treatment has been given to 5 of the 28 patients. In a subsequent paper on thiouracil and methylthiouracil as preoperative therapeutics a more detailed mention will be made of these five cases.

For the remaining 23 patients the average period of treatment with methylthiouracil has been 111 days.

With a few exceptions, the individual case histories will not be cited separately. The anamnestic data on the patients include no facts of particular interest.

### *Grouping of the Patients.*

*A. Operated Patients:* 4 women, aged 27—57, and  
1 man, 40 years old, all with

clinically severe — moderate thyrotoxicosis: exophthalmic goiter in 4, thyrotoxic adenoma in 1.

Average period of treatment with methylthiouracil: 55.6 days (25—109 days).

In all the cases the course of the operative treatment was uncomplicated.

*B. Non-operated Patients:* 7 women, aged 21—52 years, with  
clinically severe — moderate thyrotoxicosis: exophthalmic goiter in all 7.

In all these 7 patients the thyrotoxic symptoms subsided under the treatment. They all state they are feeling well able to do their usual work. Apparently the therapeutic results are quite satisfactory.

The average period of treatment with methylthiouracil in the hospital has been 29.6 days. After their discharge from the hospital they have been given ambulatory treatment. For the sake of control, at intervals of 2—7 weeks, they have been readmitted for one day.

The effect of the treatment on the weight and metabolism is evident from Fig. 3. The question of dosage will be dealt with in a separate section below.



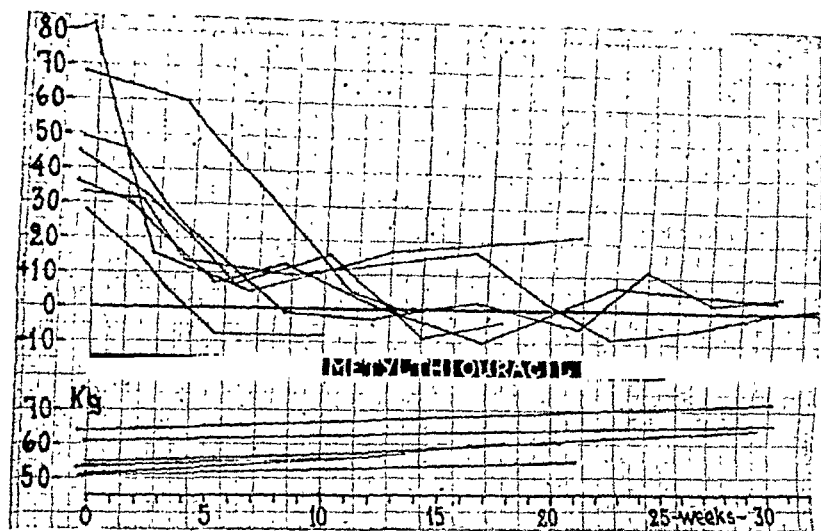


Fig. 3. Weight and metabolism curves for 7 patients with severe — moderate exophthalmic goiter, treated with methylthiouracil.

C. *Non-operated Patients:* 7 women, aged 25—62 years, and 2 men, aged 51—52, all with

*clinically slight — moderate thyrotoxicosis.* Diagnosis:

Exophthalmic goiter: 5 patients (including 1 with recurrence after subtotal thyroidectomy).

Hyperthyroidism: 4 patients (including 2 with thyrotoxic adenoma, 1 with hyperthyroidism after thyroid medication).

The average period of treatment with methylthiouracil in the hospital has been 30.8 days.

In 6 of the 9 patients the thyrotoxic symptoms have disappeared, and the patients state they are feeling well. With the exception of one patient who has been under treatment only for 5 weeks, they have all been able to resume work. Apparently the therapeutic results in these cases are quite satisfactory.

The effect of the treatment on the weight and metabolism is evident from Fig. 4.

One patient (woman, aged 51) with moderate hyperthyroidism after 8 years' abusive consumption of thyroid tablets will be men-

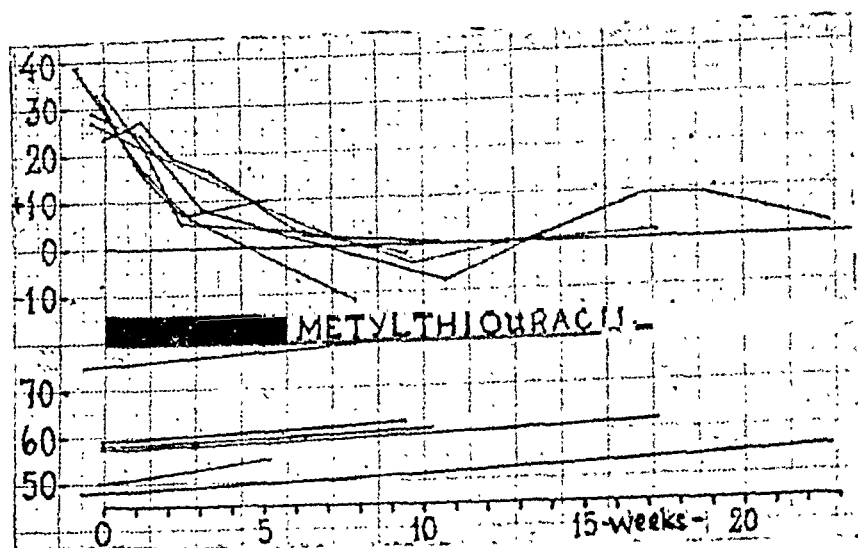


Fig. 4. Weight and metabolism curves for 6 patients with slight — moderate thyrotoxicosis, treated with methylthiouracil.

tioned further under the section «Dosage». In her case too the therapeutic result was good.

In 2 patients the treatment did not give the result desired, namely:

1. Woman, aged 62. Diagnosis: Hyperthyroidism (thyrotoxic adenoma).
2. Man, aged 51. Diagnosis: Hyperthyroidism.

In these two patients the thyrotoxic symptoms subsided somewhat, but their general condition has not become satisfactory. In No. 1 the weight has remained unchanged, while No. 2 has gained a little in weight. The effect of the treatment on the metabolism is evident from Fig. 5. The treatment is being continued in No. 1, whereas No. 2 will be operated on.

D. Special mention is to be made of 2 patients:

1. Woman, aged 53. *Clinical Diagnosis:* Hyperthyroidism (thyrotoxic adenoma); Myocardial degeneration; Cardiac insufficiency; Arterial hypertension.

On 7/2/44, treatment with thiouracil was commenced (see Fig. 6). After 12 days' treatment an exanthema appeared, accompanied by oedema of the skin. The skin lesion improved at once when the thiouracil treatment was discontinued for a single day; but it got

worse immediately on continuation of the treatment. At first the inconvenience associated herewith was only slight, and hence an attempt was made to carry through the treatment anyhow, especially as the patient was rather unsuitable for operative treatment because of her heart lesion. Gradually, however, the skin lesion got so bad that it became necessary completely to discontinue the administration of thiouracil. Before this step was taken, a try was made with discontinuous treatment — also to no avail.



Fig. 5. Metabolism curves for 2 patients with slight — moderate thyrotoxicosis treated with methylthiouracil. — See the text.

Under the treatment the thyrotoxic symptoms had practically disappeared, and the patient was feeling fairly well — apart from the skin lesion. The metabolism had fallen to + 14, and the weight was increasing.

After discontinuance of the treatment the thyrotoxic symptoms returned, and the metabolism began to rise.

After a few weeks a try was made with methylthiouracil, and — contrary to our expectation — she proved to tolerate this remedy very well. Now the thyrotoxic symptoms subsided completely, and the metabolism became normal. Since then, her treatment has been continued as ambulatory (for dosage, see Fig. 6), and she feels very well. She is able to do her own housework — even some gardening too — and she says she is better now than she has been for a good many years.

2. Woman, aged 54. *Clinical Diagnosis:* Hyperthyroidism; Heart lesion.

This patient presented the phenomenon which has been observed also in several other cases: when the treatment ceases, the thyrotoxic symptoms recur. Under treatment with methylthiouracil her thyrotoxic symptoms subsided in part, and the metabolism fell, albeit but slowly, to a normal level. On discontinuance of the methylthiouracil therapy, however, the thyrotoxic complaints

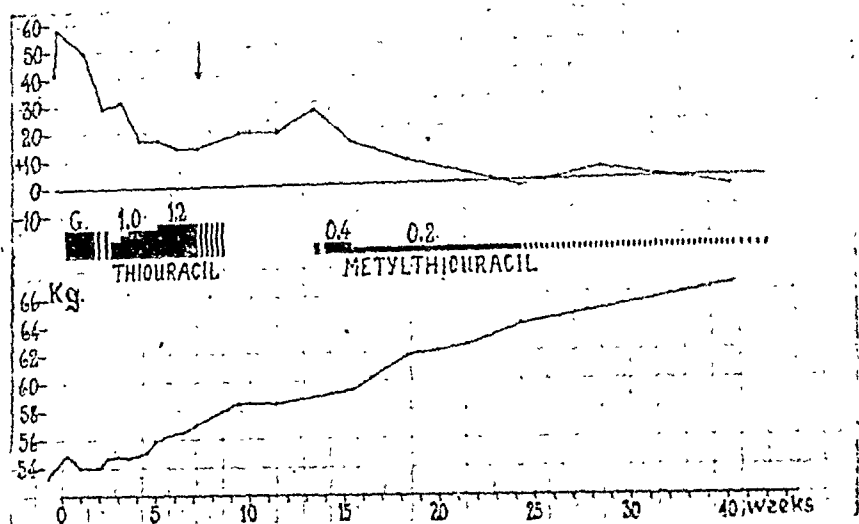


Fig. 6. Weight and metabolism curves for a woman, aged 53, with moderate thyrotoxicosis, treated with thiouracil and methylthiouracil. — See the text.

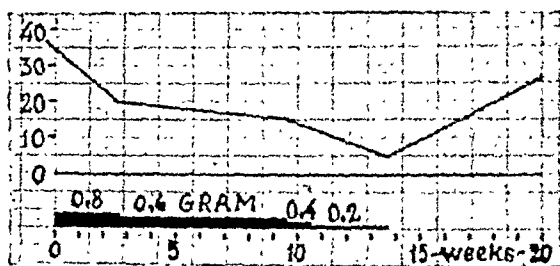


Fig. 7. Metabolism curve for a female patient, aged 54, with hyperthyroidism during and after treatment with methylthiouracil.

reappeared in a very marked degree, and the metabolism began to rise (see Fig. 7).

E. 1 patient, a woman, aged 68, in whom a rather severe degree of exophthalmic goiter persisted unchanged in spite of protracted preliminary treatment with iodine. Her case will be discussed in a special section below, together with a few of the operated patients who likewise had been given a preliminary treatment with iodine.

F. 4 patients, requiring no particular mention, as their period of treatment is yet too short to allow of any conclusion as to the effectivity of the treatment.

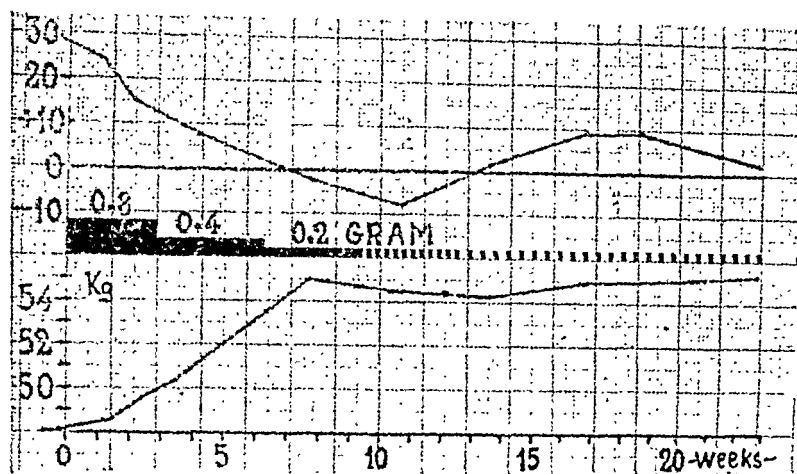


Fig. 8. Dosage together with weight and metabolism curves for a female patient, aged 32, with moderate exophthalmic goiter, treated with methylthiouracil.

### *Dosage.*

When we commenced treating thyrotoxicosis with methylthiouracil, we gave the same doses we had employed in thiouracil therapy, *i.e.*, an initial dose of 1—1.2 g daily. When the biological experiments with this substance showed plainly that its strumogenic effect is greater than that of thiouracil, we tried — with excellent result — to lower the initial dose. For, in the dosage of these remedies we have followed the principle of getting down to the minimal effective dose as soon as possible, primarily in order to avoid the risk of untoward effects.

*Initial Dose:* For initial dose we now give 0.6—0.8 g daily, in the form of tablets of 20 cg, distributed throughout the day. This dose gives an excellent effect; and many things indicate that something near the maximal effect is obtained with this dose. To give a daily dose over 0.8 g would hardly be expedient — and hardly advisable. For it would considerably increase the risk of untoward effects of a more severe character and hardly increase the therapeutic effect in any noticeable degree. For substantiation of the latter statement it will be appropriate here to mention that my biological experiments on rats show that by increasing the dosage (from 0.25 mg daily, given by stomach tube, for 15 days) we soon arrive at doses giving practically a maximal effect: for methylthiouracil, as low as

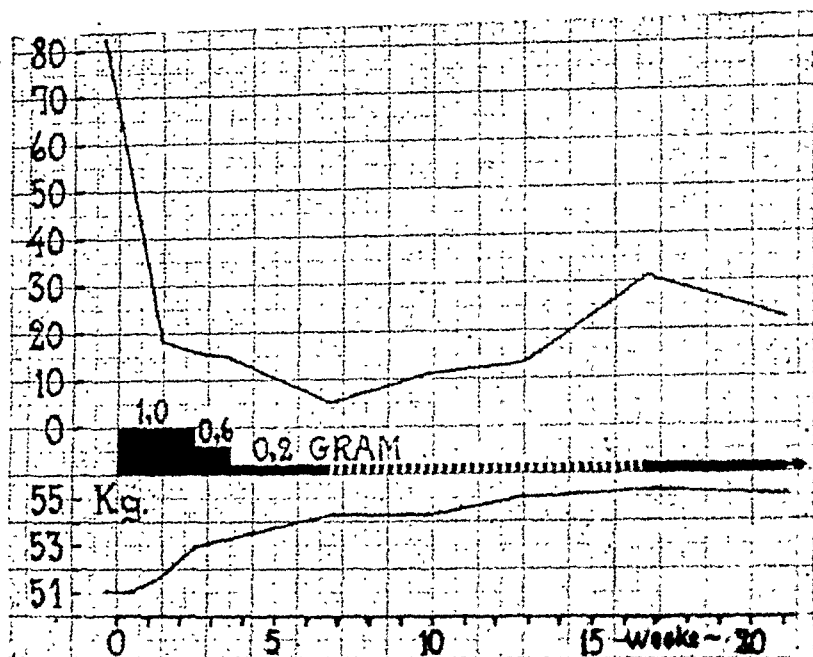


Fig. 9. Dosage together with weight and metabolism curves for a female patient, aged 39, with moderate exophthalmic goiter, treated with methylthiouracil.

about 5 mg daily for 15 days (see Fig. 1). Further increase in the dosage (up to 80 mg daily for 15 days) gives no increase in the effect worth mention.

In the *continuous treatment* with this remedy we now follow this principle:

1. As soon as a distinct effect on the thyrotoxic condition of the patient is observed under this treatment—that is, when the thyrotoxic symptoms begin to subside, and the metabolism commences to fall, while the weight begins to rise—the dose is lowered to 40 cg daily (see Figs. 8 and 9).

2. When additional improvement of the patient is established—that is, when the thyrotoxic symptoms have subsided partially or completely, and the metabolism practically has become normal—the dose is lowered further to 0.2–0.1 g daily, possibly to 0.2 g every other day.

*Maintenance Dose:* In deciding on the maintenance dose, various conditions have to be taken into consideration.

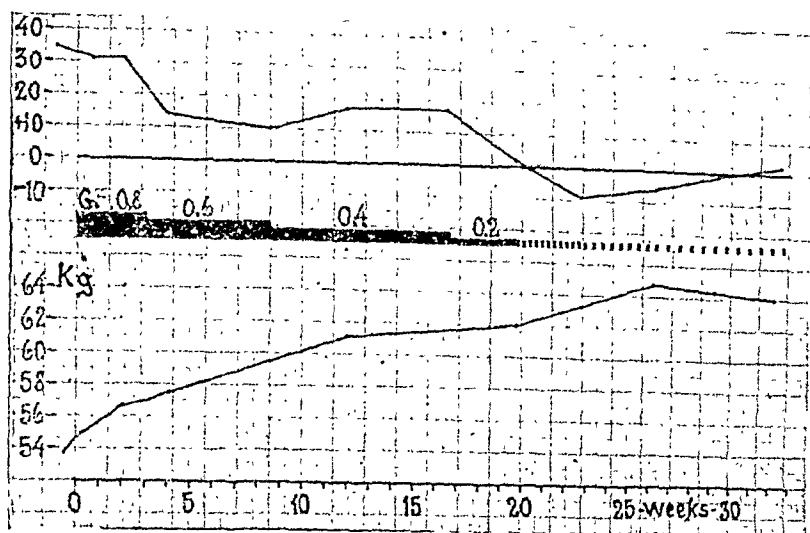


Fig. 10. Dosage together with weight and metabolism curves for a female patient, aged 25, with moderate exophthalmic goiter, treated with methylthiouracil.

In principle, we must try to find the amount of methylthiouracil that lowers the increased thyroxin production so much that only the amount required by the organism is given free. If the maintenance dose is too large, the organism is not supplied with sufficient thyroxin, the metabolism falls to a subnormal level, and the risk of myxoedema is present. When normal rats are given methylthiouracil, this remedy inhibits the synthesis of the thyroid hormone, the metabolism of the rat falls and a hypothyroid condition develops; the thyrotropic principle of the anterior pituitary lobe tries to compensate this condition by increasing the activity of the thyroid; and this results in enlargement of the glands. It is reasonable to expect that something similar would happen in man if the amount of thyroxin in the organism falls to subnormal values from overdosage of methylthiouracil.

Another aspect we have to pay attention to is the weight of the patient. Very often we see a quite considerable gain in weight under this treatment, sometimes to an undersired level. If the weight keeps increasing considerably under the treatment with a small maintenance dose, this feature in itself alone indicates that the dose still is too large (see Fig. 10).

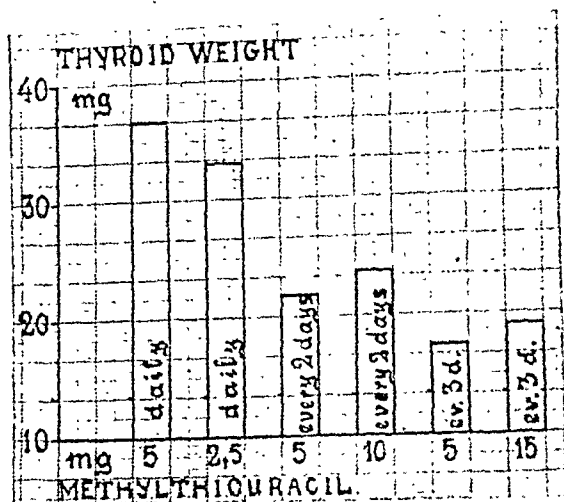


Fig. 11. Female rats, 6 months old, treated for 15 days with methylthiouracil daily, every other day, or every third day.

In this connection it will be appropriate to cite the following case history:

Woman, aged 47. *Clinical Diagnosis:* Hyperthyroidism; Climacterium; Obesity. Since the age of 25 the weight of the patient has been increasing greatly — up to 140 kg — and, on this account, through the last 8 years she has been treated with thyroid preparation, sometimes even in very large doses. In the last 5 months before her admission to the hospital, however, a moderate degree of thyrotoxicosis has developed although in these 5 months the patient was not given any thyroid substance. Under the treatment with methylthiouracil together with a reducing diet the rate of metabolism decreased, without any increase in the weight (at that time about 90 kg). Then, however, the weight began to increase, on which account the maintenance dose was lowered — with the result that the metabolism rose from a normal level to about +30.

This patient illustrates very well that sometimes we may meet with difficulties in paying regard to the metabolism as well as to the thyrotoxic symptoms and the weight.

*Size of Maintenance Dose:* It will be a matter of judgment whether one ought to choose a *daily dosage* with small amounts of methylthiouracil (0.1–0.05 g, possibly less) or a *discontinuous dosage* (0.2 g every 2 or 3 days). The biological experiments on rats show, however, that the strumogenic effect of methylthiou-



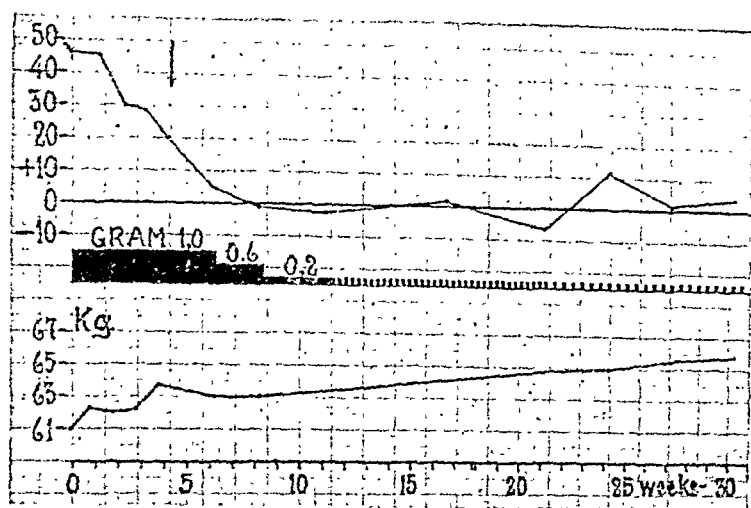


Fig. 12. Dosage together with weight and metabolism curves for a female patient, aged 39, with moderate exophthalmic goiter, treated with methylthiouracil.

racil asserts itself in a far lesser degree when a certain dose (*e.g.*, 5 mg) is given every other day for 15 days than when one-half of the dose (2.5 mg) is given daily for 15 days (see Fig. 11).

By choosing to lower the daily maintenance dose to 0.1—0.05 g, possibly even less, it may be necessary either to have tablets differing in their methylthiouracil content or to let the patient divide the tablets in several parts—which will readily jeopardize the accuracy of the dosage. Here it is to be emphasized explicitly that often the necessary maintenance dose is exceedingly small; it is also very desirable that the influence of methylthiouracil on the organism in general be as slight as possible.

In the Copenhagen County Hospital we have mostly employed the discontinuous maintenance dose (see Figs. 8, 9, 10 and 12). From Fig. 10 it is evident that as far as the metabolism and weight are concerned, the patient gets along very well on 1 tablet (20 cg methylthiouracil) every 4 days. It may be added that she feels perfectly well on this dose.

### *Significance of Iodine in the Treatment of Thyrotoxicosis with Methylthiouracil.*

The effect of iodine on the thyrotoxic condition is not due to a neutralization of, or change in, the thyroid hormone present, nor

to a change in the sensitiveness of the tissue to this hormone. On the contrary, iodine exerts its effect on the function of the thyroid gland: the thyrocytes present in a hyperplastic state are brought to quiescence, and this alters the output of thyroid hormone from the gland, promoting thus the storage of colloid (3).

The effect of thiouracil and methylthiouracil on the thyroid gland is due to an inhibitory influence on the synthesis of the thyroid hormone. This by no means brings the hyperplastic thyrocytes into a resting state — as does the iodine treatment — but the cells are prevented from giving off the same increased amount of thyroid hormone to the organism. Theoretically it should be practicable to combine the two mentioned effects on the thyrocytes. This possibility, which is of no particular interest in this connection, will be discussed in a subsequent paper.

Means (3) emphasizes that the most adequate conception of the toxic goiter will be: that an unknown factor makes the thyroid evacuate its store of colloid, and stimulates the cells of the gland in increased secretory activity. Administration of iodine by no means reduces the action of this factor. But, mechanically or chemically — or in both ways — iodine brings about the erection of a barrier that constitutes an obstruction to the delivery of the hormone to the organism. In time this barrier may be overcome partially, but as long as it exists, the amount of hormone given off to the organism will never reach the same level as in the absence of this barrier. A completely iodine-refractory state will then imply that the iodine has lost all its capacity for the formation of the barrier mentioned. But such a state may hardly occur in reality.

Here we shall not enter into the effect of iodine on the various forms of thyrotoxicosis. It is a well-known fact, however, that not infrequently we meet with thyrotoxicosis patients who fail to respond to the iodine treatment with the improvement of the thyrotoxic symptoms aimed at. If in such cases methylthiouracil therapy is instituted after a preliminary treatment with iodine, it will often be found that the methylthiouracil effect is slow in manifesting itself. Presumably this is due to the circumstance that thyroid hormone has been stored in the gland as a result of the iodine treatment. The administration of methylthiouracil is not likely to have any effect on this ready-made hormone. Only gradually, as the

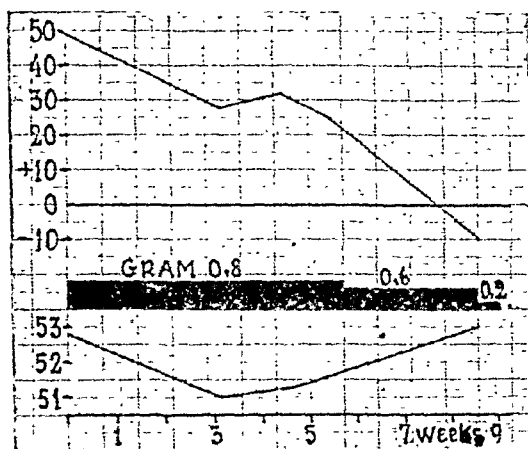


Fig. 13. Dosage together with weight and metabolism curves for a female patient, aged 68, with rather severe, iodine-treated, exophthalmic goiter, now treated with methylthiouracil.

store of hormone is being consumed, does the methylthiouracil effect appear. Theoretically, a sufficiently protracted treatment of thyrotoxicosis with methylthiouracil should always result in underbalance of the organism with regard to thyroxin.

Figs. 13 and 14 illustrate how the methylthiouracil effect often is late in its appearance in thyrotoxicosis patients who beforehand have been treated with iodine. In the patient represented by Fig. 13 — a woman, aged 68, with a severe degree of exophthalmic goiter — the iodine treatment was discontinued immediately before the institution of methylthiouracil therapy. In the case of the patient represented by Fig. 14 — a man, 40 years old, with a rather severe degree of exophthalmic goiter — the administration of iodine was continued for some time after methylthiouracil treatment was commenced.

According to the theoretical considerations above, it would be irrational to keep on giving iodine after commencement of treatment with methylthiouracil. When, nevertheless, we preferred to do so in the last-mentioned case, it was because of some sad experiences: In the preceding paper (4), mention is made of two patients in Group C. Both of them had a severe degree of thyrotoxicosis (exophthalmic goiter), and in both cases the administration of iodide was discontinued at the same time as the treatment

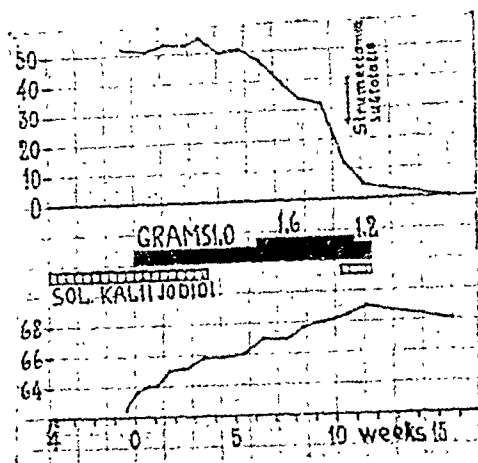


Fig. 14. Dosage together with weight and metabolism curves for a male patient, aged 40, with rather severe, iodine-treated, exophthalmic goiter, treated with methylthiouracil.

with thiouracil commenced. In both patients the institution of this treatment was immediately followed by an acute and very marked aggravation of the condition, with signs of a thyrotoxic crisis. The cause of this aggravation, which in both cases was of transitory nature, is rather difficult to perceive, as an aggravation resulting from discontinuance of iodine treatment usually appears gradually.

Our experiences appear to show that when iodine-treated patients are to be given methylthiouracil therapy, it is not advisable suddenly to discontinue the iodine at the same time as the administration of methylthiouracil commences, but either keep on giving iodine for 1—2 weeks or keep it up throughout the treatment.

#### *Untoward Effects.*

In the total 28 patients treated with methylthiouracil, untoward effects — all slight — were observed only in a few cases — namely, as follows:

<i>By-effects</i>	<i>No. of patients</i>
Transitory nausea .....	1
Bitter taste in the mouth .....	1
Rise in temperature .....	1
Exanthema .....	2

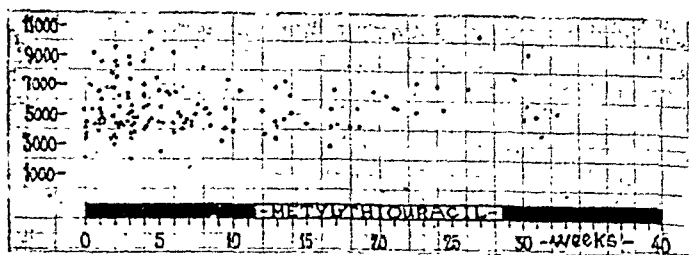


Fig. 15. White blood counts under treatment with methylthiouracil (22 patients).

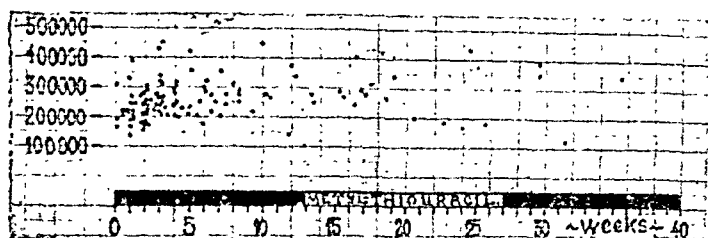


Fig. 16. Thrombocyte counts under treatment with methylthiouracil (21 patients).

When the percental frequency of by-effects in the patients treated with methylthiouracil is smaller than in those given thiouracil, the explanation undoubtedly is to be looked for in the dosage. Neither in the 12 patients treated with thiouracil nor in the present 28 patients given methylthiouracil have we seen any by-effect of a more serious character — something that is of the greatest interest and of decisive importance to the further employment of these remedies in the clinic.

### *Laboratory Examinations.*

In the present cases as well as those treated with thiouracil (4), at fairly regular intervals, various laboratory examinations were performed in order to reveal any possible untoward effects on the internal milieu of the organism due to the remedies mentioned.

*Urine:* Albumin has not been demonstrated in the urine in any of the cases under this treatment.

*Hemoglobin %:* No abnormal deviations.

*Sedimentation Rate:* No abnormal deviations.

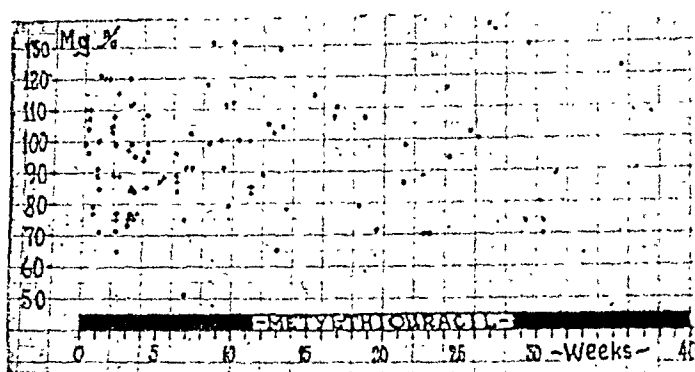


Fig. 17. Blood sugar determinations under treatment with methylthiouracil (20 patients).

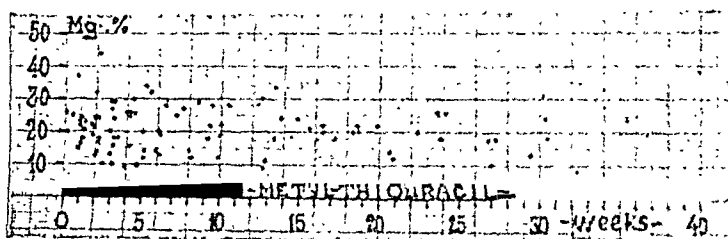


Fig. 18. Blood urea determinations under treatment with methylthiouracil (21 patients).

*Differential Count:* This was performed fairly regularly only in 6 patients, 5 of whom showed a relative lymphocytosis, which in 3 of the cases was transitory though with lymphocytic preponderance. The granulocyte count was never found to be less than 1000 per  $\text{mm}^3$ .

*Sternal Puncture:* This was performed only on 3 patients after 1—1½ months' treatment. The examination of these punctates, obligingly performed by Dr. A. Soeborg-Ohlsen, gave the same result as found in the patient treated with thiouracil, namely: lively activity of the myelocytic system as well as the erythrocytic.

*White Blood Count,* see Fig. 15.

*Thrombocyte Count,* see Fig. 16.

*Fasting Blood Sugar Concentration,* see Fig. 17.

*Blood Urea,* see Fig. 18.

*Serum Calcium,* see Fig. 19.

*Serum Cholesterol,* see Fig. 20.

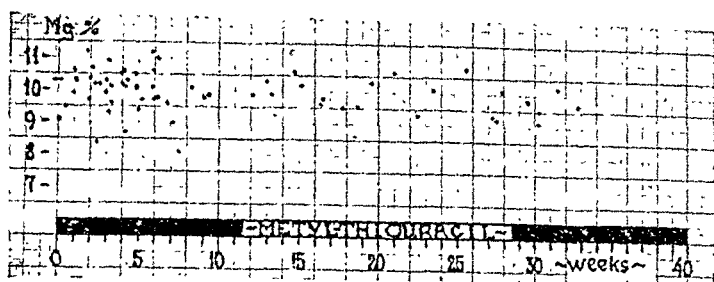


Fig. 19. Serum calcium determinations under treatment with methylthiouracil (19 patients).

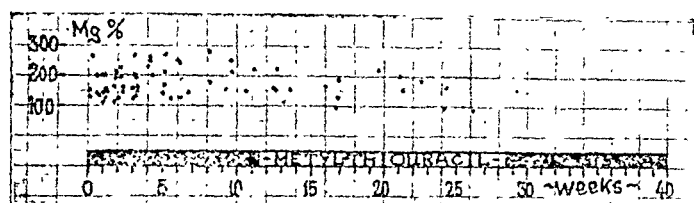


Fig. 20. Serum cholesterol determinations under treatment with methylthiouracil.

Only the serum calcium and serum cholesterol determinations are to be mentioned further. Under treatment with thiouracil (4) a considerable dispersion is seen of the serum calcium values, with values as low as 7.2 mg %, whereas under the treatment with methylthiouracil the values are far more uniform. From Fig. 19 it will be noticed that within the first 8 weeks of treatment values under 9.5 mg % were observed only 3 times; all the other values fall within the normal limit. While thus the serum calcium determinations under treatment with thiouracil gave rise to some uneasiness, this has by no means been the case under the treatment with methylthiouracil.

Under treatment with thiouracil (4) we have seen a considerable rise in the serum cholesterol values (from 100 to 330 mg %, from 250 to 500 mg %), even though this rise appears merely to have been temporary. Under the treatment with methylthiouracil, on the other hand, we have seen only an insignificant increase which at no time exceeded the limit for the normal values. In several of these patients the values remained unchanged, and in a few of the patients they even decreased a little under the treatment.

*Exophthalmus:* Only a few of the patients who have been treated for methylthiouracil for a considerable length of time have had exophthalmus in a fairly pronounced degree. Hence we are not able to say anything about the behaviour of exophthalmus under this treatment but merely state that it is our impression that the exophthalmus has shown a tendency to subside.

*Size of the Goiter:* In 12 of our patients who had a distinctly recognizable enlargement of the thyroid, the circumference of the neck was measured regularly. This together with palpation gave the following information about the size of the goiter under the treatment with methylthiouracil.

6 patients showed no change in the size of the goiter.

3 showed a very slight increase, and

3 showed a rather marked increase, in the size of the goiter.

No decrease of the goiter was observed in any case under the treatment.

*Pulse Rate:* The pulse rate was watched in all the cases and it was found to fall slowly to about normal values at the same time as the thyrotoxic symptoms subsided.

### Discussion.

Methylthiouracil as well as thiouracil are substances with considerable strumogenic effect. In rat experiments, methylthiouracil is found to have a greater strumogenic effect than thiouracil. The toxicity is nearly the same for the two substances.

Concerning both substances it may be stated that they are able with a very high degree of certainty to make the thyrotoxic symptoms in goiter patients subside and lower the increased metabolism. The establishment of this effect requires a certain latent period, which varies somewhat from one patient to another and is prolonged by preceding or simultaneous treatment with iodine. As the thyrotoxic symptoms subside under this treatment there is a fairly regular increase in the weight. The rapidity with which the thyrotoxic symptoms subside under the treatment appears to be fairly alike for the two substances.

After the favorable effect on the thyrotoxic state has been established, it is practicable to maintain it on continued admi-



nistration of the substances, whereas the symptoms reappear when this medication is discontinued. The maintenance dose required is much smaller than the initial dose. In deciding on the maintenance dose due regard has to be paid to the thyrotoxic symptoms, the rate of metabolism and the weight of the patient. Too large a dose may lead to hypothyroidism.

Now three questions suggest themselves:

1. Can the patients be made symptom-free?
2. Has the treatment a curative effect?
3. Does the treatment imply any injurious effect on the organism?

1. Most of the patients treated in this way through a considerable length of time state they are feeling well. Some are even extraordinarily enthusiastic about the treatment, claiming that now they are feeling better than they have done for many years. They are able to do their usual work without any trouble, and they lead a normal life without feeling ill in any way. On further enquiry it is found, however, that in some of the patients — albeit relatively few — the good result is merely apparent. On questioning these patients it is learned that the therapeutic result is good as long as they lead a very quiet life, but mental or physical strain brings them out of balance rather readily. We are most inclined to advise such patients to submit to operative treatment.

The question about the employment of these remedies for pre-operative treatment will be dealt with separately.

2. As yet we are unable to say whether the treatment has a curative effect. After treatment for a period of 10—11 months no sign is seen yet that indicates that the thyroid gland will enter into a resting state. In patients with enlargement of the thyroid, the size of the gland keeps unchanged or increases under the treatment. No decrease in the size of the goiter is observed. In the case of a patient who was operated on after 279 days of treatment with thiouracil, the histological picture of the thyroid showed an enormous activity of the gland.

It may be that treatment through a number of years somehow may bring the gland into a resting state, but it is still impracticable to say anything about this. Investigations must be continued in order to settle this very important question.

3. The literature has brought rather many reports on injurious by-effects appearing under the treatment, especially with thiourea but also with thiouracil. The employment of methylthiouracil has not been tried out to the same extent. The most serious of these untoward effects are leukopenia and thrombopenia which several times have led to a fatal outcome.

In our material we have seen only slight and apparently insignificant by-effects. Thiouracil has given rise to such by-effects more often than has methylthiouracil. This difference, we think, is most likely due to the fact that methylthiouracil was given in smaller doses; and it is to be emphasized most emphatically that under the treatment it is of the greatest importance as soon as possible to lower the dosage as far as practicable.

In our patient material thiouracil has given rise to an, apparently merely temporary, rise in serum cholesterol to values considerably above the normal. Under thiouracil treatment the values for serum calcium have in several cases fallen to a subnormal level; it is to be mentioned, however, that these values have not remained low, and that the patients concerned have never presented any clinical evidence of hypocalcemia. Methylthiouracil has not had any similar influence on the serum cholesterol and serum calcium values, which have remained within the normal limit (perhaps owing to the lower doses?) Neither thiouracil nor methylthiouracil has had any injurious influence on the hemoglobin percentage, sedimentation rate, blood sugar content or blood urea concentration; and albuminuria has never been demonstrated under this treatment.

In no instance have we observed an abnormally low thrombocyte count.

The white blood count has a few times given values under 3000, but these values have always increased again.

In the differential count we have often observed a relative lymphocytosis, sometimes with lymphocytic preponderance, but this relative lymphocytosis has nearly always been of a transitory nature. The granulocyte count was never seen to fall below 1000 per mm<sup>3</sup>.

Sternal puncture has invariably shown an increase in the activity of the myelocytic system or of the erythrocytic, most often of both.

The last features mentioned show that a very close control of the blood picture is important during the treatment.

From these findings it will be evident that methylthiouracil appears to be slightly superior to thiouracil in the treatment of thyrotoxicosis even though the difference in the effect of the two remedies on the state of thyrotoxicosis and the organism in general is not particularly great. In addition, however, the preparation of the methylthiouracil is far easier than that of thiouracil and on this account we have adopted the employment of methylthiouracil for the new patients admitted with thyrotoxicosis.

In thiouracil and methylthiouracil we now have two remedies which quite undoubtedly will be employed extensively in the treatment of thyrotoxicosis. In patients who are not suitable for operative treatment on account of a heart lesion or for some other reason these remedies are most serviceable; and it must also be expected that they will be employed to a very large extent in all severe cases of thyrotoxicosis, as the post-operative thyrotoxic crisis hardly may set when the patients have been set in with these remedies.

The two substances are not likely to oust the employment of iodine, but they will constitute a very valuable supplement to the use of iodine in the treatment of thyrotoxicosis.

The two substances are not harmless, however, and their clinical employment requires indispensably that patients under this treatment be examined regularly, especially with a view to changes in the blood picture.

As the initial dose necessarily is rather large, the treatment with these substances should always be commenced in the hospital.

### Summary.

In a preceding paper the writer has dealt with the strumogenic substances, especially thiouracil, their mode of action, and the employment of thiouracil in the treatment of patients with thyrotoxicosis.

Biological experiments performed by the writer have shown that methylthiouracil has a stronger strumogenic effect than thiouracil, but about the same toxicity for rats.

An account is given of the treatment of 28 thyrotoxicosis patients with methylthiouracil. The longest period of treatment in this material is 33 weeks. The substance has a considerable anti-

thyroid effect, and its employment is able with great certainty to make the thyrotoxic symptoms subside after a somewhat varying latent period, which is prolonged by treatment with iodine. The rapidity with which this takes place appears to be about the same for thiouracil and methylthiouracil. On continued administration of a small maintenance dose the symptoms may apparently be checked completely.

The question of dosage is discussed, and it is emphasized explicitly that, with a view to the possible untoward effect, it is necessary as soon as practicable to lower the dose to the least possible. The significance of iodine in the treatment with thiouracil and methylthiouracil is discussed. No serious untoward effects were observed under this treatment, merely a few instances of transitory nausea and rise in temperature, besides exanthema.

The treatment has had no noxious effect on the hemoglobin percentage, sedimentation rate, and blood urea or blood sugar concentration, nor has it given rise to albuminuria. Thrombopenia has not been observed under the treatment, nor a granulocyte count under 1000 per mm<sup>3</sup>. Sternal puncture has shown an increased activity of the erythrocytic and myelocytic systems. There has been no increase in the serum cholesterol values to any level above the normal limit, nor any fall in the serum calcium values to a level below the normal limit.

Under this treatment no decrease has been observed in the size of the goiter; and as yet there is nothing to indicate that the treatment has a curative effect.

The writer emphasizes that control examination of the patients under this treatment is very important, especially with a view to changes in the blood picture.

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(From the Medical Department B, Bispebjerg Hospital, Copenhagen,  
Chief: Professor. Dr. med. E. Meulengracht).

## Increasing incidence of Hyperthyreoidism in Denmark.

By

E. MEULENGRACHT, Copenhagen.

(Submitted for publication March 12, 1945).

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### Introduction.

At the meeting held by »Dansk Selskab for Intern Medicin» in May 1942, the author remarked in the discussion following Dr. Schiødt's paper on »Masked hyperthyreoidism», that at the Medical Department B of Bispebjerg Hospital we were of opinion that the number of cases of hyperthyreoidism<sup>1</sup> admitted to the department had increased, without the department having asked particularly for such patients, or the doctors who distribute the patients between the departments having specially sent us them. A number of the members reported that they had made similar observations.

Since then the number of patients with hyperthyreoidism has increased even more conspicuously. At one time (Sept. 5th 1942) we had 26 patients with hyperthyreoidism out of a total number of 146 patients at the department. During the autumn we have on nearly every day when we were receiving females admitted one or more patients with hyperthyreoidism, on some days three or four.

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<sup>1</sup> As regards terminology and classification, the name, hyperthyreoidism has been used synonymous with Grave's disease, hyperthyreosis, thyreotoxicosis, Basedow's disease, struma basedowifcata, toxic adenoma.

We have had as much as 7 males at the same time suffering from hyperthyreoidism, in spite of the well-known fact that male patients with this disease are usually rare. During the summer we have had 5 patients with spontaneous thyreotoxic crises (cf. Krarup's report), whilst previously several years have passed between such cases. The nurses complain that the patients with hyperthyreoidism eat so much that the rations do not suffice. Our apparatus for determining B. M. R. is overstrained.

If this conspicuous increase in the number of patients with hyperthyreoidism is due to an increased morbidity, i. e. increased incidence of the disease per population unit, we are dealing with a very interesting phenomenon indeed, but a priori we cannot exclude the possibility that the increase is due to improved diagnostics and a consequent more frequent hospitalisation of these patients. The phenomenon must therefore be examined more in detail.

### *Previous Observations on Increased Incidence of Hyperthyreoidism.*

The literature contains some few reports on increasing incidence of hyperthyreoidism, particularly in Vienna during the years following the first World War or during the midtwenties (Firgau, Wiesel, Borak, Schimak). The figures are but small, and the publications only short remarks in connection with which the authors discuss whether the preventive use of iodine in the goiter areas bears the responsibility for the increase.

A detailed study appeared from Sweden in 1935, published by Sällström: *Vorkommen und Verbreitung der Thyreotoxikose in Schweden*. This study shows plainly that during the period 1917—1932 there has been a gradual and pronounced rise in the number of hospitalised cases of thyreotoxicosis in Sweden (Fig. 1). In 1917 Kungl. Medicinalstyrelsen's reports show that 356 cases were hospitalised, whilst in 1932 the number was 1,394. The cases from the later part of the period — the years 1925—1932 — have been studied more in detail, each case having been considered separately. If the cases are divided into three groups: +++ (severe thyreotoxicosis with exophthalmus), ++ (severe thyreotoxicosis without exophthalmus), + (slight thyreotoxicosis), it is seen that the severe cases with exophthalmus have increased with 19 per cent; the

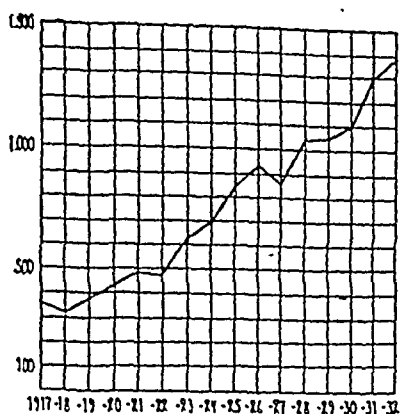


Fig. 1. After Sällström.

Curve, which shows the number of cases of hyperthyreoidism reported to the Kungl. Medicinalstyrelse during the years 1917—1932.

severe cases without exophthalmus with 100 per cent., and the slight cases with 150 per cent. (Fig. 2).

Sällström draws the conclusion that the increase is mainly due to the following three factors:

- 1) Improved diagnostics.
- 2) A greater tendency towards hospitalising the patients.
- 3) A significant increase in number of patients? The fact that a rise has also been found in the severest cases, though only of 19 per cent., speaks in favour of this point.

The present author has found a single report by Plummer on a transitory, so to speak «epidemic», increase in thyreotoxicosis. The report is cited after Means, as the original has not been available: «Plummer (1931) makes the interesting claim that in certain portions of the upper Mississippi Valley and the Great Lakes region a sudden increase in the incidence of toxic goiter, an epidemic in fact, occurred in the years following 1923, reaching a peak in 1926 and 1927, then receding to the 1923 level by 1931. He draws this inference from the number of cases coming to the Mayo Clinic, especially from Olmsted and other Countries in close proximity to Rochester and from which the majority of the cases in the entire community are sent to the clinic. He also expresses his belief in the probability that there were waves of higher incidence following the influenza epidemics of 1899 and 1918. At the height of the last

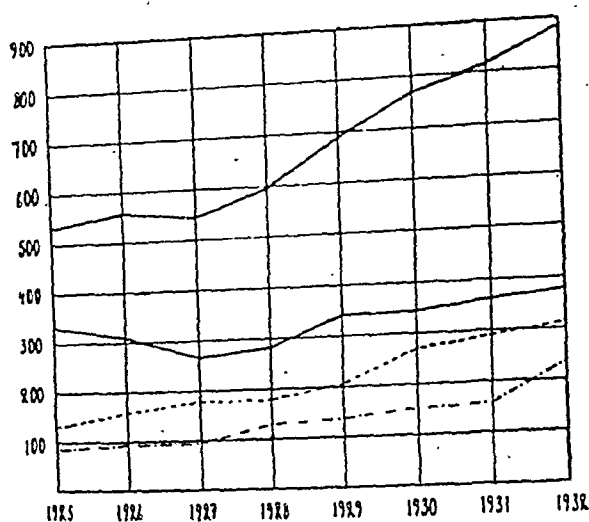


Fig. 2. After Sällström.

The incidences of the total group of hyperthyroidism and of the sub-groups (+ + +, + + and +) during the years 1925—1932.  
 — the total data, — group + + +, ---- the group + +, -.-.- the group + (Abseissa: years, ordinate: number of cases).

so-called epidemic he believes that the incidence in the regions stated rose to three to four times that of any preceding period. He further states that he does not believe that the introduction of iodized salt was responsible for the »epidemic».

#### *Author's Own Observations.*

The author has tried to throw more light on the subject, as far as it is possible, by examining a limited area with obligatory access to hospitals, namely the municipality of Copenhagen.

Table 1 (Fig. 3) shows the incidence of hyperthyroidism, as found in the reports from the Medical Departments of the Copenhagen municipality during the ten-year period 1921—1930. It is seen that during these years there is no significant rise in the number of patients admitted to the departments in question, which in the said period almost monopolise the admission of patients with the said diagnose from the Copenhagen municipality, only a few patients with these diagnoses having been received at Balder's Hospital, the Øresundshospital or the Blegdamshospital.



Table 1.

Number of patients with hyperthyreoidism according to the annual reports from the Kommunehospital departments II and III, and Bispebjerg Hospital departments B and C, 1921—1930.

1921	42
1922	50
1923	59
1924	58
1925	49
1926	50
1927	61
1928	51
1929	40
1930	59

The following ten-year period, the years 1932—1941, is quite different; the figures have been put down in Table 2 (Fig. 4).

The table shows a gradual and very pronounced rise during the period, which is more easily seen in Fig. 4. During the years 1939 and 1940 there is a temporary fall, which no doubt is connected with a less common tendency towards hospitalisation during the first years of the present War, during which years some of the departments in question had partly closed down for reason of war-preparedness. But otherwise the number of patients increases gradually and strongly, the total number having increased by about 250 per cent. during the said period.

The same increase has been seen at the Medical Out-Patient departments; but whilst the out-patient department of the Kommunehospital only receives patients from the municipality of Copenhagen, the out-patients department of the Rigshospital also receives patients from other parts, and the latter is therefore not illustrative of the area to be examined here.



Fig. 3. Number of cases of hyperthyreoidism according to the annual reports from the Kommunehospital, departments II and III, Bispebjerg Hospital, departments B and C, 1921—1930.

Table 2.

Number of patients with hyperthyreoidism according to the annual reports from Bispebjerg Hospital departments B and C, the Kommunehospital departments II, III and VII, and Sundby Hospital, 1931—1941.

Except for Sundby Hospital the figures give males + females.

The numbers in brackets from the first years at department II, the Kommunehospital, indicate that the disease was regarded as a complication only to some other affection.

The medical department at Sundby Hospital was opened in 1933.

	BBH B	BBH C	KH II	KH III	KH VII	SH	Togeth- er
1931	0+9	0+15	2+9	(3) 1+3	0	÷	42
1932	1+17	0+6	2+12	(2) (2) 3+5	0+3	÷	53
1933	1+21	1+14	3+13	(2) (4) 1+6	0+2	3	71
1934	2+23	0+8	1+10	(1) (3) 1+9	2+8	25	93
1935	6+21	5+5	3+9	(3) 2+8	2+5	22	91
1936	2+20	2+9	0+9	2+11	0+9	50	114
1937	3+16	0+14	1+15	1+17	1+11	74	153
1938	0+21	1+15	0+12	1+18	3+3	75	149
1939	3+26	2+13	1+4	4+8	2+12	62	137
1940	2+25	0+14	0+12	0+5	4+12	36	110
1941	1+42	2+24	2+21	4+2	7+12	54	171

Now, it goes without saying, that data taken from the annual reports are raw data. In the first place there is a possibility that the diagnostic criteria and the registration principles vary from department to department. Furthermore the figures include re-admissions, both to the same department and to other departments, the same patient possibly being registered several times. Further, there is a certain, small number of patients belonging to the Copenhagen area which are not included, namely the patients admitted to the private hospitals, to the Finsensinstitut and to the Rigshospital, which latter partly receives patients from the area of Copenhagen. We may, however, seemingly reckon, that these relationships are of the same order of size from year to year.

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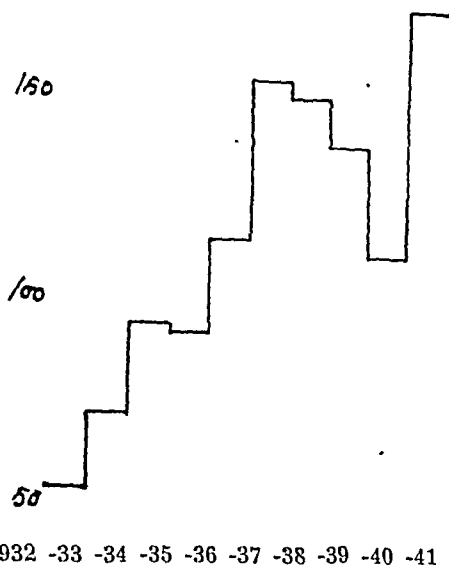


Fig. 4. Number of cases of hyperthyroidism according to the annual reports from Bispebjerg Hospital, departments B and C, the Kommunehospital, departments II, III and VII and Sundby Hospital, during the years 1931—1941.

The year 1942, in which, as mentioned above, we are of opinion that the increase in the incidence of hyperthyroidism has been particularly conspicuous, is not yet ready to be treated in the annual reports. Therefore so far I have had to deal solely with the data from our own department.

Table 3. gives the *revised* data from the Medical Department B. of Bispebjerg Hospital from 1932 till Dec. 1st 1942, and Fig. 5 gives the corresponding distribution. (The cases have been recorded according to the day they were discharged). The figures have been revised as follows: All the case records from the said period have been handled, and the records with the diagnoses Mb. Basedowii, hyperthyroidism or the like, have been laid aside. Then the latter records have been reviewed critically. The criteria for Mb. Basedowii have been: The usual clinical symptoms as well as a B.M.R. of 120 per cent. or more. Patients with a doubtful diagno-

Table 3.

Revised number of patients according to the annual reports from Bispebjerg Hospital, medical department B.

1932	15
1933	12
1934	18
1935	17
1936	12
1937	16
1938	16
1939	22
1940	21
1941	34
1942	ca. 118

sis have not been counted, nor have cases of recovered Mb. Basedowii (Mb. Basedowii antea). Cases of goiter, which have turned to hyperthyreoidism, have been counted, but they are only very few. In case of re-admission, only the first admission has been counted. In this manner the number has been reduced as compared with the figures of the annual report, but this is first of all due to the elimination of the re-admissions.

The table and the curve show that at our department the rise

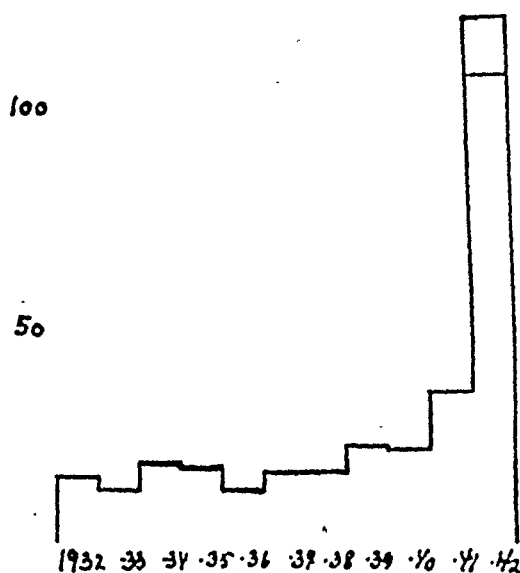


Fig. 5. Revised number of patients with hyperthyroidism from Bispebjerg Hospital, department B 1942 (the number for Dec. has been estimated).

during the years 1932—1941 has been small in comparison with the total rise for all the Copenhagen departments, but this is perhaps due to the fact that Sundby Hospital has received so many of these patients. Otherwise the most conspicuous feature of the figures is the sudden jump with which the figures rise in 1942, in which year the number of patients is 5—6 times that of the previous period. It must be said that neither during the ten year period nor in 1942 has there been a corresponding rise in the number of cases of none-toxic goiter.

### Discussion.

First the gradual rise during the years 1932—1941 will be discussed.

It is immediately seen that the rise is greater than corresponding to the increase in population. According to information from the Municipal Statistical Department of Copenhagen the population of the Copenhagen Municipality was 631,890 on Nov. 1st 1932 and 702,424 on Nov. 1st 1941—i.e. the increase has been about 10 per cent.

On the other hand, the general tendency towards sending patients to hospital has increased considerably during the period. In 1932 (April 1st 1931—April 1st 1932) the Statistical Year Book for Copenhagen shows that 38,413 patients in all were received at the Municipal Hospitals of Copenhagen (+ the private clinics and hospitals used by the municipality), whilst in 1940 (April 1st 1939—March 31st 1940) the corresponding figure was 52,647. The increase was gradual. The number of patients at the said medical out-patient departments has almost been doubled during the period. This increased tendency towards sending patients to hospital in general may also to a certain degree have influenced the number of patients with hyperthyreoidism. It cannot, however, have played any decisive part; in the first place the tendency has not by far increased corresponding to the increase in number of patients with hyperthyreoidism hospitalised, and secondly we think it justifiable to reckon that almost every patient in the Municipality of Copenhagen in whom the diagnosis of hyperthyreoidism is made or suspected, will be sent to hospital, independently of variation in the general tendency towards hospitalisation.

It would therefore be of far greater influence on the number of patients sent to hospital if the attention of the physicians in general had been drawn to this *facies morbi* and they therefore were more liable to make this diagnosis. We must therefore ask: Is there any reason to believe that the doctors of Copenhagen are more liable now to make the diagnosis of hyperthyroidism or to ventilate it than they were ten years ago? The answer to this question is undoubtedly: Yes.

Determination of the B.M.R., was, it is true, also used previously, but it is within the last ten years that it has become commonly used, not only in the hospital departments, but also amongst the practising physicians, particularly through the S.O.L. (The laboratory of the Panel Doctors' Organisation), and as regards the influence of this upon the diagnosis we can only expect it to act gradually as the doctors through determination of the B.M.R. grow accustomed to the fact that loss in weight, lack of emotional balance, tendency towards diarrhoea, cardiac trouble, particularly perpetual arrhythmia, etc., may be symptoms of hyperthyroidism, even though ocular symptoms and goiter are little pronounced or completely absent. We must therefore reckon that part of the increase during the ten-year period is due to improved diagnostics.

We cannot from the present data, in the form in which they are presented here, draw any definite conclusions as to whether the morbidity has also been increased during the said ten-year period. In order to decide this it would be necessary to go through each case and group the cases according to their severity, as Sällström has done it, Sällström surely being right when he concludes that an increased morbidity would also result in an increase of the severe cases, which we must reckon would at any time of the period have been diagnosed. Now an older clinician will say that to day patients with hyperthyroidism present a less severe *facies morbi*, different from what they did 20—25 years ago, at which time ocular symptoms and goiter were seemingly far more frequent, but this is probably due to the diagnosis previously only having been made on patients with these conspicuous symptoms — it was before the time when we made determinations of the B.M.R. — But this is long before the ten-year period we are dealing with here, and as far as I can directly estimate, the proportion between the severe and the less severe cases has not changed so much during

the period that it can account for the rise of 250 per cent, as would be the case if this rise was only due to improved diagnostics, and this estimate is very decisively supported by the following report by Schmith and Krarup. I therefore feel justified in reckoning that an increase in the number of patients admitted of 250 per cent. within the ten-year period definitely indicates that there has been a true increase in morbidity.

I shall now deal with the jump that has occurred during the present year. This increase must no doubt indicate something that is different from the gradual rise during the previous ten years.

It is true that the data have only been collected at a single department, the total figure from the Copenhagen Municipality cannot be obtained until the annual reports have been worked out. The distributing doctor, however, declares that the increase cannot be due to any change in the distribution of patients between the departments and that these patients have not been specially sent to our department; this view is verified by remarks from other medical departments, who all declare »we are full up with hyperthyreoidism». Corresponding remarks are heard from practitioners, from the surgical departments which operate upon the patients with hyperthyreoidism, and also to a certain extent from the neurologic and psychiatric clinics.

It must be considered as out of the question that this sudden enormous increase should be due to a suddenly improved ability to make the diagnosis. And it is not only the less severe cases which have increased in incidence. It is a characteristic fact that amongst the patients received during the last year at our department, 80 per cent. had been sent to the hospital under the diagnosis of hyperthyreoidism or the like. The above-mentioned fact that during the last year we have had five cases of spontaneous thyreotoxic crises also shows that not all our cases have been slight; and further the symptoms seem to be the same as those found in our patients with hyperthyreoidism during the ten-year period 1932—1941 (see the following paper by Schmith & Krarup).

Thus, all facts seem to indicate that the sudden increase in 1942 is really a pronounced increase in morbidity, and the question arises, whether we can in any manner explain this phenomenon.

Regarding the etiology of hyperthyreoidism, we know that the genotype plays a not unimportant part; this is seen from the

heredity, which is pronounced and has recently been discussed (Bartels). We do not know whether other exogenous factors may play their part — but if we are dealing with a true rise in morbidity, this *must* be the case.

As it is known, the emotional factors have often been strongly pointed out in this connection. But I cannot see that because emotional factors are of importance in the history of the patients, we are justified in concluding anything regarding the etiology; it is a matter of course that when a disease has a period of latency of varying length, during which emotional lability is a pronounced symptom, the patients themselves will often reckon that the onset of the disease dates from psychic shock, without this necessarily being the true onset of the disease. Therefore, if it is contended that the War with its anxiety and grievances is the cause of the present accumulation of hyperthyreoidism, I will answer that in the first place it has not so far been proved that emotional factors play any primary part as etiological factor in hyperthyreoidism, and secondly that such factors do not seem to be particularly frequent in the history of our present patients. As far as possible I have personally asked the patients. A large number of them have stated that they have not had any particular sorrow or grievances — neither do they give such an impression — other patients themselves relate their disease to some emotional experience or other, but this does not seem to happen more frequently than previously. Further it is worth noticing that so far we have not received any information about similar rises in the morbidity from the countries which are regularly at war, and this was to be expected if the emotional factors played the decisive part. Neither during the war 1914—1918 were corresponding rises in incidence observed.

The question naturally rises whether anything in the nutritional conditions caused by the war may be the cause, but regarding such factors we are without knowledge of any kind.

One thing must be taken into account, and that is the iodized salt. As it is known, the question whether iodized salt may cause hyperthyreoidism has been of great importance in the goiter areas, but I have not been able to find any convincing publications. Means has reduced the whole question of «iodine hyperthyreoidism» to an absurdity.

In this country, at any rate in Copenhagen, iodized salt has to



an increasing extent been used as table salt, particularly Kelp iodine salt. This salt is liked because it is finely granulated and is therefore nice for table use. It is not used for cooking.

I have asked some of the patients with hyperthyreoidism, and some patients without hyperthyreoidism, which kind of salt they used. 14 out of 35 patients with hyperthyreoidism had used iodine salt for a longer period or occasionally, whilst 48 out of 220 none-hyperthyreoidism patients had used the salt correspondingly. This gives 40 and 22 per cent. resp., but the figures for the hyperthyreoidism group are so small, that I do not feel justified in regarding the difference as decisive.

I have some analyses of various samples of iodized salt (Mr. K. W. Jackerott, Kontrollaboratoriet):

1 kg	Kelp iodized salt contains	.....	16 mg KJ
1 kg	»	»	»
1 kg	»	»	»
1 kg	»	»	»
1 kg	»	»	»
1 kg	C. Thyge Ludvigsen & Co. iodine dry salt contains	.....	15 mg »

From the Kelp iodine salt factory I have been informed that an iodine compound is added to the salt which results in a total of 13 mgs iodine per kg.

We thus see that 1 kg iodized salt only contains some few mgs iodine, and that if a person consumes e.g. 1 gram of table salt daily, it will take him three years to consume these few mgs of iodine. Thus, one must believe in homoeopathics, if one is to think that these doses are of any consequence to the present question. The quantity of iodine in Kelp iodine salt corresponds to what is found in natural ocean salt or stone salt, but the iodine evaporates during the preparations which the salt goes through before it is sold as cooking salt.

As we know, we have had two extraordinary cold winters — colder than we have had for over 100 years. Sällström states that in Sweden there are more cases of hyperthyreoidism in regions with a continental climate than with an insular climate. I will leave open the question, whether the climatic conditions in this country have been of any importance.

As it is known, the question of a relationship between hyperthyroidism and an infection has also been discussed, in this country by Sølling. As regards this point we cannot say anything in connection with the present accumulation of cases.

It is therefore my opinion that we will do best in just registering the fact that we have at present an «epidemic» of hyperthyroidism, and observe the phenomenon carefully, but admit that so far we are not able to explain it.

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From Department III (Medicine), the Kommune Hospital, Copenhagen  
(Chief Physician: Poul Iversen, M. D.)

## Angiospastic Encephalopathy.

By

KNUD BRØCHNER-MORTENSEN.

(Submitted for publication February 14, 1945).

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### Introduction.

Even at a rather early juncture attempts were made to divide the symptom complex of uremia into various groups.

In 1845 Moore (47) reported a case history with chiefly cerebral symptoms that in perspicuity comes up to the most modern descriptions of angiospastic encephalopathy.

In 1895 Senator (71) gave an excellent description of the acute uremia, »urämische Eklampsie«, with various uremic equivalents (among others, the earliest accounts of transitory pareses and hemiplegia), and of the chronic uremia in its various forms. In agreement with his contemporaries, however, Senator thought that the various forms had the same pathogenesis, saying: »Ob die Urämie acut oder chronisch verläuft, wird wohl davon abhängen, ob die Ueberladung des Blutes mit schädlichen Stoffen plötzlich eintritt oder sich allmählich entwickelt«.

With this statement Senator subscribed to the theory originally advanced by Wilson (86) in 1833: that the various symptoms of uremia are due to intoxication with the toxic substances retained on account of the kidney lesion. Notwithstanding the very comprehensive investigations carried out subsequently, it has not yet been settled conclusively which substances bring about this intoxication (31, 79, 80).

In contrast to this *chemical* theory, in 1861 Traube (74) advanced the *mechanical or anatomical* theory, according to which

the uremic symptoms are attributed to cerebral oedema from hy-dremia. The oedema theory was soon thrown into the background, however, especially after Cohnheim had established that absence of cerebral oedema was a frequent autopsy finding in patients who died of uremia. Now the chief importance was again attached to the changes in the blood and tissue fluids owing to retention of the urine, whereas the cerebral oedema that was observed occasionally was considered a concomitant phenomenon — perhaps of inflammatory nature.

A few authors, especially Rosenstein (67) (1894) tried to combine the chemical and the mechanical theories, assuming that among the urinary elements retained there were some substances which gave rise to anemia of the brain through arteriospasm with or without oedema.

When Traube's theory was not adopted by his contemporaries, it was primarily because at that time uremia was still looked upon as a nosological unity, and ardent search was made for a pathogenesis common to its various manifestations.

Towards the end of the last century a few authors (66) expressed some doubt about this unity. Still, to Ascoli (3) (1903) goes the credit for being the first to emphasize that the various clinical pictures of uremia hardly may be due to a common cause. In his lectures he reviewed a variegated lot of case histories and concluded that *«eine allgemeine Erklärung der Urämie . . . nicht möglich und statthaft ist»*. After this, he set up two groups: *«Urinämie»* and *«renale Urämie»*. The first group comprises the following symptoms: mental and physical debility, confusion, dyspnea, stupor, and coma; these phenomena were ascribed to the substances retained. The second group comprises the symptoms: hypertension, eclamptic attacks, pareses, amaurosis, etc. — and they were attributed to certain cytotoxins or nephrolysins, substances assumed to arise in the injured kidney tissue.

In France, in 1903 and following years, Widal (85) and collaborators carried out some extensive clinical and experimental studies, on the basis of which they suggested a pathogenetic division of the uremic manifestations into *«le syndrome azotémie»* and *«le syndrome chlorurémie»*. Oedema of the brain with the resulting cerebral symptoms was attributed to retention of chlorides.

In the meantime, Peabody (55) (1891) and Rosenstein (67) (1894) had advanced the hypothesis that the cerebral symptoms of uremia might be due to vascular spasm, but this theory was first formulated more precisely by Pal (53, 54) in the beginning of this century.

In Germany, in the years after the appearance of the works of Ascoli, the concept of uremia underwent further division when Reiss (59, 60, 61) and, especially, Volhard (78, 79) set up the three types: 1) true uremia (retention uremia), 2) eclamptic uremia, and 3) pseudouremia. In eclamptic uremia the symptoms were assumed to be brought about by oedema of the brain, whereas in pseudouremia the symptoms were assumed to result from vascular spasms.

In its typical form, the *eclamptic uremia* (which Volhard originally designated as acute pseudouremia) reminds of epileptic seizures. Often, but not always, it is associated with certain prodromal symptoms: headache, dizziness, nausea, vomiting, paresthesias. At the same time there is a rise in the blood pressure.

After this, in the more severe cases, the patient soon becomes unconscious, and clonic convulsions make their appearance; most often they are universal, but they may be unilateral or shift from one region to another. The convulsion lasts from seconds to minutes, and often it reappears several times in the following hours. As a rule the patient is pale, with cyanosis during the convulsive attacks, the breathing is stertorous, and there may be foam about the mouth. Often the pupils are dilated, the tendon reflexes are greatly accentuated, and Babinski's sign is often positive. There is an additional rise in the blood pressure, which is increased beforehand.

After the attack the patient may present hemiplegia or isolated pareses, aphasia, amaurosis, disturbances of the hearing or mental changes. Usually these phenomena subside rapidly — within some hours. In a few cases they are seen to last longer, sometimes turning into permanent rest-symptoms in the form of isolated paresis, paresthesias or scotoma.

Occasionally transitory attacks are seen of paresis, amaurosis, aphasia, etc. in patients without eclampsia, and these phenomena are then designated as eclamptic equivalents.

Eclamptic uremia appears preferably in patients with acute or subacute glomerulonephritis, but it may be encountered also in patients with increased blood pressure from some other cause.

In *pseudouremia* we meet with more chronic symptoms: headache (often of migraine-like character), dizziness, fatigue, lowered capacity for concentration, impairment of the memory, insomnia, irritability and depression. But sometimes we also meet with symptoms appearing in attacks that in some degree resemble the eclamptic equivalents in the acute eclamptic uremia: brief fainting spells, disturbances of the vision, hearing and speech, mental changes, and attacks of Cheyne-Stokes' breathing. These phenomena may be merely of brief duration but most often they are more protracted than in eclamptic uremia. In many cases the clinical picture at first resembles a cerebral hemorrhage. The attacks appear most often in elderly patients with arterial hypertension and arteriosclerosis.

In U. S. A., finally, Oppenheimer & Fishberg (51) (1928) suggested the term »hypertensive encephalopathy» as a common designation for these clinical pictures, as they held that it is not practicable like Volhard with certainty to distinguish between two forms of non-azotemic uremia; besides, the clinical picture of the lesion may be of a more acute or more chronic character. In both cases the pathogenesis is assumed to be an ischemia due to arteriospasm, sometimes with secondary oedema. Usually the term »hypertensive encephalopathy» is employed. In a few cases (6), however, the term »angiospastic encephalopathy» has been used. Presumably the latter term is preferable — in analogy with angiospastic retinitis.

Some neurologists have objected to the establishment of these nosographic entities, emphasizing that these cases often differed widely in the pathologic-anatomical foundation for their clinical manifestation (34, 76, 87).

### Pathogenesis.

#### *The Kidney Function.*

After the clinicians — in particular through the works of Volhard — had got so far as to differentiate the cases here mentioned from the old uremic syndrome as a special pathogenetic unity, it has become the prevailing view that the encephalopathy in its acute form as well as the chronic is not dependent upon the functional state of the kidneys.

The study of the renal function with reliable functional tests has shown that the most pronounced forms of angiospastic encephalopathy may occur in patients without any kidney lesion, and that in patients with kidney affections there appears to be no correlation between the degree of a possible impairment of the kidney function and the frequency, duration and intensity of the acute cerebral symptoms.

In mechanical obstruction of the urinary passages the encephalopathy is very rare.

There is no doubt, however, that in certain cases the impairment of the kidney function may act as accessory pathogenetic factor. Thus retention of water may increase or bring about the cerebral oedema which undoubtedly plays a role in the acute form of the encephalopathy. But the water retention is not the only decisive factor, and the encephalopathy is very rare in nephrosis — where the water retention is particularly marked.

Something similar applies to the salt retention, to which particular importance has been attached by French investigators (40, 85). As a rule, however, water and salt retention will not be due to lowering of the kidney function.

### *Arterial Hypertension.*

Even at an early juncture the clinicians were aware that the cerebral symptoms of the old uremic syndrome were closely associated with hypertension. Subsequent experiences have shown that in the various forms of angiospastic encephalopathy the appearance of the cerebral symptoms generally is preceded by a rather considerable hypertension, and that a rather marked rise in the arterial pressure, especially the distolic, is found in immediate connection with the attack.

In children with glomerulonephritis Blackfan (7, 8) found the eventual cerebral symptoms to appear when the systolic pressure reached over 140 mm.

It is reasonable, then, to assume some causal connection between the cerebral symptoms and the hypertension — or the phenomena bringing about the hypertension.

This is further confirmed by the similarity between angiospastic encephalopathy and the cerebral symptoms of eclampsia in preg-

nancy and saturnine encephalopathy. In eclampsia of pregnancy the convulsive attacks are invariably accompanied by hypertension, whereas the kidney function as a rule is unimpaired. Also lead encephalopathy is often associated with hypertension — and the convulsions and amaurosis increase and decrease with the variations in the blood pressure (39, 53, 77).

Thus Labadie-Lagrave & Laubry (39) observed a patient with acute lead poisoning who became blind when the systolic pressure reached 250 mm. Amyl nitrite lowered the pressure to 170 mm. simultaneously with the return of the vision. An hour later the amaurosis returned, and then it again subsided slowly as the blood pressure gradually returned to normal level.

It is not all cases of lead encephalopathy, however, that are accompanied by hypertension (16, 18).

Evans (16), for instance, has seen convulsions in a patient with lead encephalopathy, in whom no increase in the blood pressure could be demonstrated at the time of the attack, but the retina showed a considerable degree of vasoconstriction.

In keeping with the more recent theories mentioned, below it has been assumed that the patients showing no increase in blood pressure during the attacks are liable to arteriospasm in the retina and the brain, but not in the splanchnic field and other places.

In analogy with this, then, it will be reasonable theoretically to assume that, depending on the extent of the arteriospasm, we might also meet with cases of angiospastic encephalopathy with hypertension during the attacks and a normal blood pressure outside the attacks — possibly even with cases in which the attacks were not associated with any increase in the blood pressure.

Indeed Kennedy, Wortis & Wortis (37), Barfred (4) and others have mentioned instances of transitory hemiplegia, etc., in patients with arteriosclerosis but without hypertension.

### *The Cerebral Oedema Theory.*

It is an old-established experience that a pronounced oedema of the brain now and then is observed in patients who died of uremia.

This observation, as mentioned, was especially emphasized by Traube (74) in 1861, who took it to be the cause of the cerebral symptoms in the uremic syndrome — in particular, the eclamptic



attacks. Traube thought the convulsions were due to an anemia of the brain brought about by the oedema, especially when this was localized to the mesencephalon, whereas oedema of the hemispheres resulted in uremic coma.

This oedema theory was supported by a few other investigators (65) but before long it was forced into the background, and it was not adopted again till Ascoli (3), Reiss (59, 60, 61) and, especially, Volhard (78, 79, 80) through their investigations had arrived at a clinical differentiation of the old uremic syndrome. Now the cerebral oedema is generally taken to be the cause of the symptom complex which, as suggested by Volhard (78, 79), is designated as »eclamptic uremia», while Oppenheim & Fishberg (51) designate it as »acute hypertensive encephalopathy».

The pathogenetic significance of this oedema has been substantiated through a great number of observations.

1. Autopsy on patients who died with these acute eclamptic phenomena has often revealed a more or less pronounced oedema of the brain (7, 8, 30, 79, 80). The weight of the brain may be increased considerably, the gyri are found to be flattened, the ventricles are compressed to mere slits, and in the more severe degrees of oedema the cerebellum may be deformed conically through pressure against the foramen magnum (7, 8). Also the pia may be markedly oedematous. In some case, on the other hand, no oedema is found on autopsy (13, 18, 54). In this connection it is to be emphasized that the post-mortem changes may be difficult to interpret as in some degree they will depend on the position of the head of the patient at the time of death and after. Furthermore, the influence of the agony on the post-mortem findings may be incalculable. As pointed out by Volhard (79), the increase in the volume of the brain will be most conspicuous on examination of horizontal section of the brain *in situ*.

2. On spinal puncture these patients usually show marked increase in the pressure that is assumed to be due to an increase in the volume of the brain — not, or only in a lesser degree, to an increase in the amount of cerebrospinal fluid.

In the cases where the cerebellum, as mentioned above, is pressed down against the foramen magnum, the spinal fluid pressure may still be normal or even lowered. Under these conditions the evacuation of spinal fluid may be associated with a consid-

erable risk and ought to be performed only under simultaneous measuring of the pressure.

Thus Gorke & Töppich (30) have reported the case of a patient with corrosive sublimate nephrosis, in whom the spinal puncture showed a pressure of 45 mm. mercury. After evacuation of a small amount of spinal fluid, there was an additional fall in the pressure; and the patient died suddenly. Autopsy showed that the brain was pressed firmly down against the foramen magnum.

In patients with eclampsia of pregnancy, Zangemeister (90) has found a high intracranial pressure *intra vitam* (by trepanation) as well as *post mortem*.

3. It is a common clinical experience that ingestion of fairly large amounts of water in patients with acute glomerulonephritis may induce acute eclamptic attacks (17, 43, 79, 80).

In experiments on dogs with administration of a large amount of water Rowntree (68) has seen a considerable increase in the intracranial pressure associated with convulsions, and on autopsy he found oedema of the brain.

In keeping herewith, it is emphasized as an indisputable clinical observation, that the eclamptic attacks may be prevented successfully by putting the patients on a diet poor in salt and water (43, 50).

In 80 patients with war nephritis who were given water *ad libitum*, Nonnenbruch (50) observed 16 cases of acute angiospastic encephalopathy, whereas after restriction of the water supply only 1 case was observed among several hundred patients. Furthermore, this only patient is said shortly before the onset of the convulsive attack to have disobeyed the directions and taken large amounts of water.

The manifest eclamptic phenomena are further combated with a fair degree of certainty by intravenous, peroral or rectal administration of hypertonic solutions of glucose or magnesium sulphate, which are assumed to draw water from the tissues — *in casu*, the brain tissue — out into the blood stream.

4. In a few cases eclamptic phenomena have been described in patients suffering from nephrosis (30, 40, 46, 49). But such isolated instances — «museum specimens» — dug out of an extensive world literature and cited again and again are not very convincing. Furthermore, a more thorough and critical review of the original reports will often show that the documentation in the individual

cases has been rather thin. The same applies to the frequently cited instances of Quincke's oedema in eclampsia (58, 64, 72).

Still, some authors are yet inclined to deny the cerebral oedema a decisive importance to the appearance of the eclamptic phenomena. Thus Lichtwitz (42) emphasizes that cerebral oedema without eclampsia is a frequent observation while, conversely, no oedema may be demonstrable in several patients with »eclamptic uremia» and that convulsions are practically never seen in patients suffering from nephrosis — the oedematous affection par excellence.

The details in the development of the cerebral oedema are still obscure. It is not simply just a part of a universal oedema, as this condition most often is absent or inconspicuous in such patients.

Some investigators, in particular of the French school (40, 85) have attached considerable importance to the assumed shifts in the osmotic aspects on account of the chloride retention, but this assertion appears not yet to have been substantiated conclusively. Other authors have imagined that the increased blood pressure in these patients brought about a high spinal fluid pressure and an increase in the amount of intracranial fluid. But neither clinical nor experimental investigations (5, 25, 38, 82) have been able to confirm this decisively.

On the other hand, the spinal fluid pressure is largely dependent on the increase in venous pressure, as may be observed directly on exertion of abdominal pressure and in Queckenstedt's experiment — and has been demonstrated experimentally by many authors (5, 32, 82). Still, an increase in the venous pressure will not give rise to particularly pronounced cerebral phenomena, and usually no increase in venous pressure is found in patients with angiospastic encephalopathy.

It is now the prevailing view that the cerebral oedema encountered in patients with hypertensive encephalopathy results from an ischemic injury to the capillaries owing to arteriospasm, and it has been compared to the oedema which accompanies angiospastic phenomena in the retina.

### *Cerebral Vasoconstriction.*

Judging from the evidence now available it seems reasonable to assume that arterial hypertension is the result of an increase in the tonus of the peripheral arterioles over large areas, but as yet

we know but little or nothing as to whether the cerebral blood vessels are involved in this process.

Various authors — in particular Pal (54) (1905) — have advanced the idea that the increased tonus of the arterioles present in hypertension would dispose to localized vascular spasms.

These spasms occur *generally* («arterial high-pressure crises») or *regionally* in various isolated vascular fields: peripherally (the «dead fingers» and crural cramps of patients with hypertension), in the coronary arteries (angina pectoris), in the mesenteric vessels (angina abdominis), and in the retinal vessels (angiospastic retinopathy). Similar cerebral vascular spasms are taken by several authors to be the cause of the cerebral symptoms in hypertensive encephalopathy.

The theory about the cerebral vascular spasms was advanced already towards the end of the past century, first by Peabody (55) (1891) and shortly after by Rosenstein (67), who thought that uremia was associated with a retention of substances which produced anemia of the brain by arteriospasm with or without oedema. Correspondingly, it had been assumed previously that the convulsions in eclampsia of pregnancy were due to vascular spasms in the kidneys and brain, elicited by the labor pain — just as also lead encephalopathy was assumed to be due to cerebral anemia (66).

Corresponding considerations were advanced by Pal (53, 54) who likewise emphasized the resemblance between the symptoms in lead encephalopathy and the cerebral symptoms in uremia, saying: «Die Erscheinungen sind bei der Urämie im wesentlichen dieselbe wie wir sie bei schwerem Bleikolik sehen». Numerous subsequent investigators have subscribed to this view, and the theory has been adopted widely, in particular after Volhard (78, 79, 80) had published his works.

Volhard assumes that circulatory disturbances owing to the vascular spasms constitute the pathogenetic factor common to the eclamptic and pseudouremic phenomena. He stated that the circulatory disturbances due to the vascular spasms may be generalized or localized, permanent or transitory, and commence suddenly or insidiously.

In circulatory disturbances with acute onset the changes in the permeability of the capillaries will often be predominant and bring about the appearance of cerebral oedema and, by this, an increase

in the intracranial pressure. Hydrostatic factors are claimed, however, to be able to influence the localization of the oedema and thus of the symptoms too.

If the circulatory disturbances develop more gradually or become particularly pronounced, the cerebral vasoconstriction and ischemia will predominate. The phenomena may make their appearance through general increase in the vascular tonus without arteriosclerosis, but it may also appear in localized arteriosclerosis without generalized vasoconstriction.

Sometimes we may meet with mixed forms of the two types and the symptoms may be accentuated by water retention owing to the presence of a kidney lesion. Renal insufficiency seems to promote the appearance of the angiospastic phenomena, but this need not be associated with retention of vasoactive substances, but rather with an increased production of such substances.

Oppenheimer & Fishberg (51) subscribe to the considerations set forth by Volhard, but they do not think that the two forms are differentiated so distinctly. In arterial hypertension the cerebral vessels as a rule are involved in the universal arteriole-constriction in such a manner that the blood-flow through the brain and the pressure in the cerebral capillary keep at somewhat normal levels. When the increase in pressure is particularly sudden or violent, however, this regulation may fail in one of two ways:

- 1) If the contraction of the cerebral arterioles is not so strong that it corresponds to the general rise in the arterial pressure, the pressure in the cerebral capillaries will increase, and this may give rise to oedema.

- 2) In various regions the cerebral arteries or arterioles may react with such pronounced spasms that ischemia appears, resulting in focal cerebral symptoms. This happens especially when the vessels are arteriosclerotic, as arteriosclerosis disposes to spasms.

These ideas have now been adopted generally, but, as emphasized by Volhard (79), modern research in this field has not advanced very far yet, so that this view still may hardly be said to have got above the level of the hypothesis.

In the last decades a great deal of work has been carried out in studies on the circulatory aspects of the brain in order to obtain an experimental and exact empirical foundation for the clinical

theory concerning the appearance of the cerebral vascular spasms and their significance to the various symptoms of the angiospastic encephalopathy.

Anatomically and physiologically, the cerebral vessels differ in several respects from other vascular fields. From a teleological point of view nature may be said above all to have provided for the blood supply of the brain.

As is wellknown, the more essential part of the blood flow to the brain goes through the basilar artery and the internal carotids, which jointly form the so-called circle of Willis, wherefrom the blood is distributed to all the six chief arterial stems of the brain. This ensures the blood supply of the brain even if one of the afferent vessels — for instance, one of the internal carotids — should become blocked. Furthermore, there is an anastomosis with the external carotid through the ophthalmic artery.

While previously the cerebral arteries were taken essentially to be end-arteries (Cohnheim), more recent investigations have established the presence of an abundant network of anastomoses. Thus, in studies on cat brains Campbell (10) has demonstrated anastomoses between large arteries, especially in the pia, numerous anastomoses between the precapillary arterioles and plentiful capillary anastomoses.

Histologically the cerebral vessels are characterized by the elastic membrane being thicker here than in other arteries. With advancing age this layer undergoes hypertrophy and is divided into two or more laminae. This is of particular importance on account of the relative weakness of the outer layers.

The grey substance of the brain is provided with considerably more capillaries than is the white substance, about 600—1000 mm per mm<sup>3</sup> as against 200—300 mm (14, 27) Roughly, the number of capillaries is proportional to the oxygen consumption (27).

The blood supply of the brain is subject to a very fine regulation in which several different mechanisms participate:

Our knowledge concerning the regulatory factors is of a rather recent date, and until recently the observations in this respect have been rather conflicting. In the later years, however, this aspect of the cerebral circulation has been elucidated on several points. Extracerebral factors play a very great role. Still, it may now be considered established that an intracerebral regulation

exists too; and chemical agents (especially  $\text{CO}_2$ ) play a considerable role in this regulation. The presence of cerebral vasomotors appears to have been established with certainty, but evidently they play a somewhat minor role.

Generally the extracerebral regulatory mechanism will not only ensure the blood supply when there is a tendency to anoxemia, but also ensure against congestion.

The variations in the arterial blood pressure appear to be of overwhelming importance to the blood perfusion of the brain, and hence this too is subject to the influence of the various blood-pressure-regulating mechanisms, the sinus caroticus and other reflex regulators (84, 88).

The influence of variations in the blood pressure on the caliber of the cerebral vessels has been investigated in various ways — with somewhat varying results.

Fog (22) measured the changes in the diameter of the pia vessels in cats after experimental increase in blood pressure (intravenous injection of adrenalin, stimulation of the splanchnic nerves or compression of the abdominal aorta) and found in most of the cases a moderate vasoconstriction of the small arteries. The lower the initial blood pressure, the more pronounced was the vasoconstriction. A sudden great rise in blood pressure, however, was able to overcome the regulation and give vasodilation. Regulation of the tonus persisted after bilateral division of the cervical sympathetic branches and all the vasomotor nerves from the aorta and carotid sinus. — Conversely, a fall in blood pressure was associated with vasodilatation (19, 20).

Changes in the chemical composition of the blood affect the arterial diameter in a marked degree. This applies in particular to universal or local changes in the  $\text{CO}_2$  content of the blood. An increase in the  $\text{CO}_2$  content gives dilatation, especially of the pia vessels, in a lesser degree of the intracerebral vessels (41, 69, 89).

A similar effect is seen after administration of various drugs (especially nitroglycerin, amyl nitrite, acetyl cholin, ether and alcohol) (69).

Various investigators have obtained somewhat deviating results with direct application or intravenous injection of adrenalin.

On measuring the diameter of the pia vessels after direct application of adrenalin in cats Fog (21) found contraction of the larger

arteries, but no measurable changes in the diameter of the small arterioles. Quite the same result was obtained after intravenous injection of adrenalin when the arterial pressure was kept constant.

As far as I have been able to find out, the vasomotor innervation of the cerebral vessels proper has not been investigated thoroughly, but studies on the pia vessels have been reported by several authors (23, 24, 69).

Stimulation of the cervical sympathetic fibers gives a unilateral vasoconstriction independent of the simultaneous changes in the arterial pressure. But the contraction involves only arteries with a diameter over 50  $\mu$ , and it is considerably less pronounced than the changes observed in the capillary diameters obtained with the same experimental technique (in a proportion of about 1:10). Conversely, stimulation of the parasympathetic fibers gives dilatation of the pia vessels.

The various regulatory mechanisms as a rule appear to be very finely coordinated. Usually the capillaries of the pia — the cerebral blood vessels which have been studied most often — are always seen to be open; the diameter of the arterioles changes but in a slight degree, and the blood flow through these vessels is remarkably constant (23), changing hardly in any measurable degree on changes in the activity in the brain — for instance, in changing from wakefulness to sleep.

In the various physiological experiments as a rule the changes observed have been so small that it seems reasonable to assume that the vasomotor activity of the cerebral vessels is too weak to be able under ordinary circumstances to produce any real anoxemia. Spasms and complete obliteration of the vessels appear to occur only on direct thermic, electrical or mechanical irritation of the normal vessel wall.

So even though various clinical observations have been taken as evidence of extensive angiospasm in the brain, no experimental findings have lent support to the view that such reactions may be produced neurogenically.

Still, it is possible, or even very likely, that the matter stands differently when the vessels are the site of morbid changes (18, 57).

Under various pathological conditions, especially in epilepsy, rather pronounced vascular phenomena have been observed in attacks which occurred under trepanation. In epileptics, Penfield



(56) found seizures associated with sudden cessation of a visible pulsation of the cerebral artery and congestion, less frequently pallor of the pia, and sometimes post-convulsive arterial spasms. In epileptics Kennedy, Wortis & Wortis (37) observed ischemia of the cortex prior to a seizure; and this phenomenon has been reported by several other authors. In contrast hereto, as far as I have been able to find out, no thorough and definite observations have been reported on the vessels of the brain in patients with angiospastic encephalopathy.

In the absence of such direct observations and indisputable experimental findings, a number of arguments have been advanced in support of the assumption that hypertensive encephalopathy is due to cerebral arteriospasm.

In the discussion of this question, great importance has been attached to the changes observed in the diameter of the retinal vessels in patients with angiospastic encephalopathy. Several investigators have observed that in these patients a transitory amaurosis or scotoma is associated with spastic obliteration of the retinal vessels and that this obliteration ceases when the visual disturbances subside.

Thus, as early as 1897, Wagenmann (81) observed vascular spasms in the retina during attacks of amaurosis in an elderly man.

Similar findings have been reported in patients with lead poisoning (15, 16, 39, 53) and eclampsia of pregnancy (33).

Furthermore, clinicians have pointed out that the angiospastic pathogenesis is rendered probable by the sudden appearance and cessation of convulsions, pareses, amaurosis, etc., and the rapid shifts in the cerebral symptoms.

Osler (52) thus described the case of a patient in whom numerous attacks of monoplegia and hemiplegia, besides amaurosis, set in suddenly and disappeared rapidly through a period of 5 years.

Chauffard (12) observed a patient in whom the convulsions shifted quickly from one side to the other.

Fishberg (18) has reported the case of a patient with glomerulonephritis, in whom the convulsions sometimes appeared in one extremity, sometimes in two.

Further, as an argument in favor of the angiospastic pathogenesis, the fact has been pointed out that the blood pressure increases considerably in direct connection with the attack.

It has been emphasized that in angiospastic encephalopathy some of the symptoms corresponded to the findings in experimental anemia of the brain (produced, for instance, by ligation of the four cerebral arteries) and also to certain features seen in many morbid conditions accompanied by cerebral anoxia (acute cardiac insufficiency, heart block, severe paroxysmal tachycardia, carbon monoxide poisoning, cyanide poisoning, strangulation, etc.).

Finally it has been pointed out that the cerebral phenomena sometimes disappeared under medicamental treatment with vasodilating remedies (69), corresponding to the observations concerning the retinal changes.

As mentioned above, in the pathogenetic interpretation of the cerebral phenomena considerable importance has been attached to their fleeting character. Indeed, this applies to most of the cases but not infrequently there appears to be a gradual transition to irreparable conditions — owing to thrombosis or hemorrhages into the brain tissue. It was this gradual transition that led Volhard (79, 80) to call attention to the more recent conception of the pathogenesis of the cerebral hemorrhage (48, 62, 63, 70, 83).

According to this, in contrast to the earlier view, the cerebral hemorrhage is not due to a direct rupture of the blood vessels (the mechanical theory), for this would not lead to the extensive deterioration of brain tissue. Often a large hemorrhage is surrounded by small hemorrhages. The primary process is assumed to be deterioration of the brain tissue with necrobiosis of the cells and of the walls of the small blood vessels.

Now Volhard (79, 80) thinks transitory angiospastic phenomena may be precursors of the apoplectic attack, and that quite similar changes may be seen in cerebral embolism and thrombosis. Thus we meet with quite gradual transitions between the various cerebral manifestations of the hypertension.

### *Conclusion.*

As is evident from the preceding, our present knowledge concerning the pathogenesis of these cerebral phenomena is very defective. Their appearance is not dependent on changes in the kidney function. They turn up chiefly in patients with hypertension, which is further increased during the more acute manifestations,

but quite similar phenomena seem to be able to appear in patients with a normal blood pressure. Oedema of the brain is found in several cases but this is no constant finding, and at present it is the prevailing view that the cerebral oedema results from an ischemic injury to the capillaries. On the whole, it seems most likely that these phenomena appear as a result of a cerebral vasoconstriction, even though the experimental foundation for this view as yet is rather slim.

It therefore seems natural indeed to employ the term »angiospastic encephalopathy» for this clinical syndrome — in analogy with the term angiospastic retinopathy.

It is reasonable to assume that the vasoconstriction constitutes the common basis for the encephalopathy in its various clinical types, and it seems doubtful whether it may be justified to maintain the sharp distinction made by Volhard between the types »eclamptic uremia» and »pseudouremia». It seems more likely merely to involve a difference between clinical manifestation of the same pathological phenomenon, the cerebral vasoconstriction.

According to the modern conception of the pathogenesis and pathological anatomy of the cerebral hemorrhage, there also appears to be a fairly gradual transition between the chronic form of angiospastic encephalopathy and the manifest permanent damage to the brain in cerebral hemorrhage and thrombosis.

Even though we thus assume a common pathogenesis for these phenomena, it may perhaps be of some importance, especially with a view to the prognosis, as far as practicable to make a clinical differentiation.

The characteristic acute attack, appearing in patients with acute glomerulonephritis — and corresponding to Volhard's eclamptic uremia — might perhaps be designated as »eclampsia nephriti-corum», in analogy with the designation »eclampsia gravidarum»

The term angiospastic encephalopathy might be employed for cases corresponding to Volhard's »chronic» pseudouremia, which occurs especially in patients with arteriosclerosis and hypertension; in their clinical features and, especially, in their course, these cases differ from the manifest hemorrhage or thrombosis of the brain.

### Writer's Clinical Observations.

In the Medical Dep. III of the Kommune Hospital, Copenhagen, in the period from July 1943 to September 1944 altogether 16 patients have been treated under the diagnosis angiospastic encephalopathy. This material includes only patients with pronounced symptoms (see case records). The total number of patients admitted to this department in this period was 2476. By measuring of the blood pressure in 2369 of these patients, a systolic pressure of more than 200 mm. mercury was found in 92 patients and a pressure of 160—200 in 286.

Of these 16 patients 9 were women and 7 men, while the proportion between women and men in the total number of patients for this period was about 8: 10.

The average age of the patients was 60 years (1 was 43 years. 9 were 50—59 years, 4 were 60—69 years, and 2 were 76 years old). About half of the patients were rather obese.

Six of the patients were admitted in direct connection with the acute attacks, while 4 entered the hospital 1—4 weeks after the onset. In 6 patients the symptoms had been present several times through a period of 1—10 years.

During the attacks, *unconsciousness* was observed in 8 patients.

*Convulsions* occurred in 2 patients (Nos. 8 and 10) — in both cases as clonic convulsions in the arms and legs. Only in one of them were the convulsions accompanied by unconsciousness.

*Pareses* occurred in 10 patients, sometimes in the form of *monoplegia*, sometimes as *hemiplegia*. Among the cases in which the paralysis appeared repeatedly, its localization shifted in some patients, while it remained constant in others. In some cases the pareses lasted a few minutes, in others a few hours, and then they disappeared rather suddenly and completely. In one patient there was a rather sudden improvement after a couple of hours and then the rest-symptoms subsided slowly. In some cases the symptoms subsided but slowly, so all sorts of transitions were seen between rapid and slow disappearance of the symptoms. The neurological examination, which usually was performed on one of the first days after admission, revealed no abnormality in 8 patients. Among the remaining 8 patients, 3 presented pareses or impairment of muscular power, 6 showed abnormalities of reflexes

(in 2 this was limited to a positive Babinski's sign) and 1 patient presented sensory disturbances.

*Aphasia* occurred in 4 patients, in 3 of whom it soon disappeared, while in the fourth it persisted for about 1 month although varying markedly in degree.

*Severe disturbances of vision* occurred in 5 patients: transitory blindness of brief duration in 2; transitory blindness with persistent paracentral scotoma in 1; gradual impairment of vision due to increasing retinopathy in 1; and thrombosis of the central vein of the retina in 1.

*Severe disturbances of the hearing* did not occur in this material.

*Paresthesias* occurred in 4 patients. 2 of them had frequent attacks of paresthesias of the fingers, in 1 they were localized to the left leg, and in 1 patient paresthesias appeared in the left arm and leg 3 weeks before a left-sided hemiplegia.

*Paroxysmal dyspnea* occurred in 2 patients. In 1 (No. 11) it appeared together with a left-sided hemiplegia which disappeared within a couple of hours. The other patient (No. 1) had repeated attacks of violent dyspnea, and she died during one of these attacks; autopsy showed perivascular oedema and perivascular hemorrhages together with tigrolysis of the ganglion cells, especially round the middle of the 4' ventricle. Volhard (79) has emphasized the paroxysmal dyspnea as an eclamptic equivalent presumably due to arteriospasm in the vicinity of the respiratory center.

*Dizziness* occurred in 8 patients, in attacks or more constantly. Of other relatively constant symptoms, *headache* occurred in 9 patients, marked *impairment of the memory* in 1, *insomnia* in 2, *depression and irritability* in 3. Several patients showed various vague mental changes in the days following the attacks, and these changes were noticeable particularly to the relatives of the patients; in other cases the mental habitus was apparently quite unaffected.

The spinal fluid was examined in 14 cases, as a rule in the morning after admission of the patient, in a few cases later. On measuring of the pressure in prone position in 13 of these patients, the initial pressure was found to be 390 mm. water in 1 patient (No. 8), 320 mm. in another (No. 7). After evacuation of 5 cm<sup>3</sup> the pressure in these 2 patients was 230 and 250 mm, respectively. In 5 patients the initial pressure was between 220 and 290 mm. In 1 of these five

patients the evacuation of 5 cm<sup>3</sup> of spinal fluid reduced the pressure from 290 to 230 mm; in the remaining 4 patients the pressure was lowered to values between 190 and 140.

In the remaining 6 patients the initial spinal fluid pressure was between 135 and 190 mm. In 2 of them evacuation of 5 cm<sup>3</sup> of fluid lowered the pressure respectively from 190 to 60 mm and from 135 to 60 mm, but both of these patients showed a normal rise and fall in the pressure in Queckenstedt's test (and this applies to all the 11 patients examined in this way).

The evacuated spinal fluid was examined in the Neurological Laboratory of the Kommune Hospital.

On protein determination after Bisgaard's method, 2 patients (Nos. 11 and 6) showed globulin values of 2 and 4, respectively, and albumin of 15 and 30. All the remaining patients showed globulin values of 0 or 1, and albumin values between 9 and 20, including 7 values over 12 (15 in 5 patients, 18 in 2).

The cell count showed 0/3 cells per mm<sup>3</sup> of spinal fluid in 7 patients, 1/3—3/3 in 5, and 6/3 in 2.

In all 14 patients the spinal fluid gave a negative Wassermann reaction. 1 of these patients (No. 6) gave positive reactions for syphilis in the blood (Wassermann 5, Kahn 7, Meinicke strong). In all the other 15 patients the Wassermann reaction in the blood was negative.

The total outcome of these spinal fluid examinations may then be summed up as follows: 3 patients showed a high spinal fluid pressure, and after the evacuation of 5 cm<sup>3</sup> of fluid the pressure still kept at a level over 200 mm water. It is to be mentioned, however, that the spinal fluid was not examined in the strictly acute phase of the encephalopathy, during which presumably an increased pressure would have been found in more patients. 2 patients showed a moderate increase in globulin, and several patients a slight increase in albumin. The cell count was normal in all the patients examined.

*Eye Examination:* Ophthalmological examination revealed vascular changes in 15 of the 16 patients: distinct arteriospasm in 8, change in caliber of the arteries in 8, compression of veins at the crossings in 11. Hemorrhages were found in 6, exudate in 4. Among the 3 patients in whom the systolic blood pressure at no time was seen to exceed 200 mm mercury, distinct arteriospasm were

found in 1. Changes in caliber without spasms in 1 (No. 12) who was examined 2 days after the attack, and a normal background of the eye in 1 (No. 9) who was examined 4 days after the cessation of the attack. If the examination had been performed during the attack, which in the last 2 cases was rather acute, it possibly would have shown arteriospasm.

In most of the patients the pupils were found to be of medium size. In 2 patients (Nos. 7 and 11), the pupils were markedly dilated and reacted to light but sluggishly on admission of these patients, respectively 1 and 3 days after the attack; but later on the pupils were normal.

**Blood Pressure.** On admission a blood pressure over 200/100 mm mercury was found in 13 patients. In 4 of them the high values peristed. In 7 patients the systolic pressure fell to values between 100 and 160, while the diastolic pressure kept at a level between 100 and 120. In 1 patient (No. 7) the pressure gradually fell to 180/95 and in 1 patient (No. 13) to 165/70.

In the remaining 3 patients (Nos. 9, 12, 14) the systolic pressure on admission was found to be 160—190, the diastolic pressure 100, while later the systolic pressure was 120—145, the diastolic 65—80.

In keeping with previous experiences, the present material shows that *the increase in blood pressure is particularly pronounced for the diastolic pressure*. It further illustrates that angiospastic encephalopathy occurs also in patients without a permanent increase in blood pressure.

Only in a few cases has there been an opportunity to examine the patients in immediate connection with the attacks, and hence the material gives no information about the interesting question whether angiospastic encephalopathy may appear without a rise in blood pressure in the phase of the attack. Theoretically, as mentioned, it would be reasonable to assume that this might be the case when the arteriospasm were localized to a narrow region.

**Kidney Function:** Measuring of the urea clearance was performed in all 16 cases.

In 8 patients — *i. e.*, in one-half of the material — the values obtained kept within the normal range of variation, varying between 72 and 107 % of the normal average value. Chemical and microscopical examination of the urine showed no abnormality in 3 of

these patients; albuminuria, but no pathological form-elements, in 2; pyuria due to colon bacilli in 2; and hematuria in 1.

8 patients showed unquestionably decreased values for the urea clearance: 6 showed values between 36 and 57 %, and 2 gave values of 8 and 13 %. Chemical and microscopic examination of the urine showed no abnormalities in 2 of these cases, albuminuria in 3, and pyuria due to colon bacilli in 4.

As a part of another investigation, Dr. Hilden made determination of the diodrast clearance after a single subcutaneous injection on 14 of the patients. Values over 500 cm<sup>3</sup> (unquestionably normal) were found only in 2 patients, values between 400 and 499 in 1, between 300 and 399 in 3, between 200 and 299 in 4, between 100 and 199 in 3, and 26 cm<sup>3</sup> in 1.

Hilden's (35) normal material of 10 patients showed values between 511 and 643 cm<sup>3</sup>. In larger-normal material the values have varied between 350 and 900 cm<sup>3</sup>.

In several cases distinct dissociation was observed between the changes in the urea clearance and in diodrast clearance, the latter being lowered in a higher degree than the former. This difference has been found previously in patients with arterial hypertension (26, 29) or chronic nephritis (36), presumably signifying a decrease in the blood-flow through the kidneys resulting from vascular changes and/or lowered capacity for secretion in the tubules due to degenerative changes.

In the 3 patients who presented no abnormality in the urea clearance test and in the chemical and microscopic examination of the urine, the values obtained for the diodrast clearance were 446, 539 and 539 cm<sup>3</sup>, respectively. In these 3 patients, then, no sign of any organic kidney lesion was demonstrated, whereas changes of some kind or other were found in the remaining 13 patients.

So the present material has confirmed the previous clinical experience: that angiospastic encephalopathy may appear in patients in whom a thorough examination fails to reveal any signs of a kidney lesion.

A decrease in the kidney function, with or without pathological changes in the urine, however, has been demonstrated in a greater majority of the patients. But here, too, no correlation was found between the measures for the kidney function and the frequency, duration and intensity of the cerebral symptoms.



*Electrocardiography:* In 9 of the patients the electrocardiogram showed a preponderance of the left side; and this was the only change observed in 2 of them. Changes in the terminal complex were found in 10 patients. Auricular fibrillation was demonstrated in 3. Only 3 patients showed no pathological changes in the electrocardiogram.

### Differential Diagnosis.

As is evident from the above, the symptomatology is rather variegated and yet, after some observations it may be summarized into a characteristic nosographic entity.

In several cases, however, the differential diagnosis may be rather difficult at the first observation of the patient and require a rather thorough examination, as several different lesions may give rise to the appearance of similar morbid features. This applies to a number of lesions which may bring about such conditions as cerebral anoxia, acute cardiac insufficiency, Adam Stokes' attack, transitory auricular fibrillation, paroxysmal tachycardia, various forms of poisoning (carbon monoxide, cyanide, etc.) besides encephalitis, tumor of the brain with oedema, and cerebral embolism, hemorrhage and thrombosis. From what has been said above, it is reasonable to assume that there is a fairly gradual transition between the chronic angiospastic encephalopathy and the permanent damage to the brain in cerebral hemorrhage and thrombosis, and also between angiospastic encephalopathy and arteriosclerosis of the brain.

### Prognosis.

The prognosis is uncertain and largely dependent on the general condition of the patient. Death may occur during the more severe attacks. As a rule, frequent attacks of angiospastic encephalopathy have to be looked upon as a serious sign; various clinicians have emphasized especially the paroxysmal dyspnea as a bad omen. On the other hand, we meet with patients who have more or less frequent attacks of angiospastic encephalopathy through a good many years before they die. In several cases permanent mental changes are seen even after the first attacks.

### Therapy.

The present material has given therapeutic experiences only in a slight degree. For often the acute phase of the encephalopathy will have subsided before the patient enters the hospital.

The therapeutic methods generally employed in the acute phases are venesection, lumbar puncture and intravenous injection of various hypertonic solutions.

*Venesection* with evacuation of 500 cm<sup>3</sup> of blood ought probably to be performed in every instance of angiospastic encephalopathy, unless the patient already is very anemic. In many cases this measure will have an excellent effect even though it gives merely a moderate fall in blood pressure.

*Lumbar Puncture.* — In keeping with what has been said in the preceding, lumbar puncture should be performed only with great cautiousness and under simultaneous measuring of the spinal fluid pressure, avoiding any risk of collapse from pressure of the oedematous brain against the foramen magnum. Often the patients will feel relieved after evacuation of a few cm<sup>3</sup> of spinal fluid. Volhard (79) has reported the case of a patient with eclamptic amaurosis, in whom the sight suddenly returned during the spinal puncture.

*Intravenous Injection of Hypertonic Solutions.* — As a rule intravenous injections of a hypertonic solution of glucose or sodium chloride will bring about a fall in the spinal fluid pressure, although this usually may be followed by a considerably secondary rise, often to a level above that of the initial pressure (9, 44).

After injection of hypertonic solutions of saccharose the secondary rise in pressure is somewhat smaller (45), but various clinicians advise against the employment of this substance as it is claimed to be able to produce degenerative changes in the convoluted tubules (2).

*Magnesium sulphate* was originally employed by Blackfan & McKhann (8) and it has been recommended warmly by Fishberg (18). Adults, for instance, may be given a slow intravenous injection of 10 cm<sup>3</sup> of Sol. magnii sulfatis pro inj. D.D. (20 %) On overdosage, with threatening respiratory failure, the patient is given an intravenous injection of calcium as, for instance, 10—20 cm<sup>3</sup> of Sol. calcii gluconatis pro inj. D.D. (10 %). The mode of action

of magnesium sulphate has not been fully elucidated, but most likely the effect is due in part to relaxation of the smooth musculature of the arterial wall.

Employment of the various *vasodilating* remedies — e.g., nitrites, acetylcholin, alcohol — is well-founded theoretically, but in practice it appears to be only of slight therapeutic value. Probably the same applies to the employment of various spasmolytics of the papaverin group, of which in particular eupaverin and neupaverin have been employed. In some of the present cases we examined the relation between the variations in blood pressure and the cerebral symptom after administration of vasodilating remedies. In 1 patient (No. 6) the systolic blood pressure decreased after inhalation of 5 cg of amyl nitrite from 220 to 190 mm mercury, and simultaneously the aphasia present subsided distinctly; but this effect was merely transitory. No real and lasting favorable effect was observed in any case.

In the presence of more severe convulsions, the patient is given chloral hydrate or Somnifen in large doses.

Outside the acute attacks, ordinary hygienic diatetic measures are employed as usually in arterial hypertension. Volhard recommends a salt-free diet poor in water, but the results of this appear to be uncertain, and it means a great inconvenience to the patient.

### Summary.

In Dep. III of the Kommune Hospital, 16 patients with angio-spastic encephalopathy were admitted in a period of about one year. The case histories are given here.

In this connection, various problems are discussed, especially concerning the pathogenesis. It is emphasized that in view of our present knowledge it is most reasonable to assume that spasms of the cerebral blood vessels constitute the main factor in the appearance of this lesion.

#### *Case records.*

##### *Case 1.*

Woman, aged 43, wife of glazier. Rec. No. III, 1065/43. Admitted 13/4—23/7/43.

Since 1916, chronic glomerulonephritis. In the last half year, increasing headache and impairment of vision. Lately, repeated attacks of marked dyspnea.

*Blood Pressure:* 250/175—220/150. *Electrocardiography:* Isoelectric T waves.

*Urine:* + albumin; + leucocytes; + colon bacilli. Urea standard clearance: 7 cm<sup>2</sup>. Diodrast clearance: 36 cm<sup>2</sup>. Blood urea: 127—235—68 mg %. Plasma bicarbonate varying between 41 and 63 vol. % CO<sub>2</sub>. Serum chloride 345—383 mg %.

*Ophthalmoscopy:* Arteries of unequal caliber, relatively narrow. Veins markedly tortuous, with Gun's phenomenon. + hemorrhage. + exudate.

*Spinal fluid* not examined. *Neurological exam.:* No abnormality.

Here in the hospital the patient had numerous attacks of violent dyspnea, and during one of these attacks she died suddenly.

*Autopsy Diagnosis:* Chronic nephritis; softening of the medulla oblongata.

*Examination of the Brain* (Dr. Erna Christensen): The specimen includes 4 blocks of tissue from the brain; 2 from the medulla oblongata, 2 from the pons. Sections from the former 2 show congestion of the blood vessels, perivascular oedema and, in one area, perivascular lymphocyte infiltration. In addition, especially the posterior part of the medulla oblongata, along the 4<sup>th</sup> ventricle, presents perivascular hemorrhages, very small accumulations of red blood cells without any demonstrable connection with blood vessels. The tissue on the whole is oedematous. The nerve-cells, especially along the 4<sup>th</sup> ventricle are swollen and show tigrolysis. Also the sections from the pons show stasis and oedema, besides small perivascular hemorrhages here and there.

The level of the sections cannot be determined exactly, but those from the medulla oblongata appear to have been taken from about the middle of the 4<sup>th</sup> ventricle.

*Histological Diagnosis:* Stasis and oedema of the medulla oblongata. Small hemorrhages of the medulla oblongata; Incipient encephalomalacy.

## Case 2.

Man, aged 61, painter. Rec. No. III, 1160—43. Admitted 9/7—13/8/43.

For several years, headache, irritability and attacks of dizziness. In connection with a psychic trauma on the day of admission, the patient became confused, dizzy, with a tendency to falling, and then unconscious for a short while. No convulsions or pareses.

*Blood Pressure:* 200/140—160/100. *Electrocardiography:* No abnormality.

*Urine:* No albumin; + leucocytes, + colon bacilli. Urea clearance (maximum): 80 cm<sup>2</sup>. Diodrast clearance: 387 cm<sup>2</sup>.

*Ophthalmoscopy:* Some discalibration of the blood vessels. Gun's phenomenon +. A few tiny hemorrhages.

*Spinal Fluid:* Pressure 190; + increase in Queckenstedt's test; albumin 15; globulin 0; cells 4/3; Wassermann negative.

*Neurological Exam.:* No abnormality.

## Case 3.

Man, aged 56, workman. Rec. No. III, 1263/43. Admitted 29/7—4/9/43. 1 year ago, sudden attack of dizziness and weakness of the legs, so that the patient dropped to the ground, lasting 2—3 min. A similar attack 3 months before admission. No convulsions or disturbances of speech. Sometimes paresthesias of the fingers.

*Blood Pressure:* 230/135—190/110. *Electrocardiography:* Preponderance of the left side;  $T_1$  negative.

*Urine:* No albumin. Urea clearance (maximum): 57 cm<sup>3</sup>. Diodrast clearance: 446 cm<sup>3</sup>.

*Ophthalmoscopy:* Blood vessels characterized by arteriosclerosis; no hemorrhage or exudate.

*Spinal fluid:* Pressure 180; + increase in Queckenstedt's test; albumin 18; globulin 0; cells 2/3; Wassermann negative.

*Neurological Exam.:* No abnormality.

## Case 4.

Woman, aged 56. Wife of workman. Rec. No. III, 1370/43. Admitted 16/9—28/9/43.

In 1938 loss of consciousness and paresis of the left lower extremity for 3 days. Several attacks of transitory paresis of the left upper extremity and aphasia.

Increasing depression, dizziness and headache.

*Blood Pressure:* 220/110—190/120. *Electrocardiography:* No abnormality.

*Urine:* No albumin; + colon bacilli. Urea clearance (maximum): 33 cm<sup>3</sup>. Diodrast clearance: 250 cm<sup>3</sup>.

*Ophthalmoscopy:* Gun's phenomenon +.

*Spinal Fluid:* Pressure 290; + increase in Queckenstedt's test; albumin 15; globulin 0; cells 0/3; Wassermann negative.

*Neurological Exam.:* No evidence of any gross organic affection. Achilles tendon reflex greater on the left side. Doubtful Babinski's sign on the left side.

## Case 5.

Woman, aged 76, old-age pensioner. Rec. No. III, 1482/43. Admitted 20/9—19/10/43.

Last 4 years, moderate functional dyspnea, now and then attacks of moderate stenocardia, no dizziness. The patient has 4 times had a brief attack of unconsciousness; the last one 3 days before admission. Never convulsions or pareses.

*Blood Pressure:* 220/120—220/110. *Electrocardiography:* Preponderance of the left side.

*Urine:* No albumin; + leucocytes; + colon bacilli. Urea clearance (maximum): 39 cm<sup>3</sup>. Diodrast clearance: 288 cm<sup>3</sup>.

*Ophthalmoscopy,* 21/9: Unequal calibration of the blood vessels; Gun's phenomenon +. No hemorrhage or exudate.

*Spinal Fluid*, 22/9: Pressure 135 + increase in Queckenstedt's test; albumin 9; globulin 0; cells 0/3; Wassermann negative.  
*Neurological Exam.*: 23/9: No abnormality.

#### Case 6.

Man, aged 54, tailor. Rec. No. III, 1559/43. Admitted 15/10—4/11/43. Syphilis ascertained in 1939. 1 year before admission, paresis of the left arm, lasting about a day. On the day of admission, paresis of the right arm and leg, which soon improved somewhat. At the same time, brief impairment of the muscular power of the left arm, together with aphasia, which persisted in a varying degree.

*Blood Pressure*: 240/140—175/110. *Electrocardiography*: Low T waves.

*Urine*: No albumin; no pathological form elements. Urea standard clearance: 39 cm<sup>2</sup>. Diodrast clearance: 539 cm<sup>2</sup>.

*Ophthalmoscopy*, 9/10: Unequal calibration of the arteries; strongly light-reflecting, positive Gun's phenomenon; a single slight hemorrhage; no exudate.

*Spinal Fluid*; 6/10: Pressure 220 + increase in Queckenstedt's test; albumin 30, globulin 4; cells 2/3; Wassermann negative (Wassermann in the blood positive). Also previous examinations, in 1942 and 1943, showed a negative Wassermann reaction in the spinal fluid — in spite of strongly positive reactions in the blood.

*Neurological Exam.*; 8/10: Moderate spastic increase in tonus and accentuation of reflexes of both right extremities. Babinski's sign positive on both sides.

The patient was gradually getting worse, with periodical haziness. Now and then, pronounced Cheyne-Stokes respiration. He died on 4/11/43.

*Autopsy* revealed syphilitic aortitis.

*Examination of the brain* (Dr. Erna Christensen) showed the following features:

External examination shows marked sclerosis of the basal arteries; otherwise no abnormality. Frontal sections through the brain show numerous small areas (up to hemp-seed size) of encephalomalacia in the corpus striatum on both sides; on the right side, corresponding to the globus pallidus and putamen, an area (more than hazel-nut size) of fresh red encephalomalacia or hemorrhage.

No macroscopic abnormality is seen in the brain stem and cerebellum.

*Microscopy*: *Specimen 1*. Left frontal horn with small areas of encephalomalacia.

In the vicinity of the ventricular wall, an area of encephalomalacia is seen with numerous phagocytic cells, microglia and roundcells in the surroundings especially perivascularly; in one place this process becomes cystic, and the cavity is filled with coagulated fluid. This process of encephalomalacia is associated with medullary-sheath degeneration which extends out into the surroundings, which are the site of oedema and changes in the blood vessels with hyalinization and here and there almost obliteration of the lumina.

*Specimen 2*. Left corpus striatum, a little laterally to the midline at the chiasm.

Here several areas of encephalomalacia are seen, of the same appearance as described above. Many of the larger arteries are markedly atheromatous, with narrowing of the lumen. This applies to the blood vessels of the pia too.

In these vessels the internal elastic membrane is split into several laminae. Other arteries are contracted, especially those in the cortex.

*Specimen 3. Right corpus striatum, with a hazel-nut-sized area of encephalomalacia.*

The area of encephalomalacia is surrounded by a beginning demarkation line with proliferation of blood vessels and accumulation of numerous macrophages containing blood pigment. Otherwise the appearance of this area is the same as described above. The larger arteries in the surroundings have undergone hyalinization of the walls and partial obliteration.

*Specimen 4. Cortex from the same section of the brain.*

The leptomeninges are thickened and fibrous. The arterial walls in the pia as well as in the cortex are hyalinized and thickened, narrowing the lumina, here and there with splitting of the internal elastic membrane into laminae. Both in the grey and white substance, here and there, marked perivascular oedema. In some areas the nerve-cells are swollen with tigrolysis; in other areas they have undergone sclerosis; but many of them are well preserved.

There is no medullary sheath degeneration in sections from this specimen, and no area of encephalomalacia.

*Specimen 5. Left hypothalamus from the same section of the brain.*

Hyalinization and atheromatosis of many arteries, and perivascular lymphocyte infiltration round several of them. Some of the nerve-cells are well preserved, others show the same changes as described in Specimen 4.

*Specimens 6 and 7. Medulla oblongata in the lower half of the 4<sup>th</sup> ventricle.* No microscopically demonstrable encephalomalacia in these specimens. The arteries of the pia as well as the arteries in the brain tissue show the same changes as described in the preceding specimens. A good many of the nerve-cells are swollen and undergoing tigrolysis; but no chronic changes in the form of sclerosis are seen.

The histological examination of the brain (and examination of the spinal fluid) has revealed no evidence of a syphilitic lesion. The numerous small areas of encephalomalacia appear to be of vascular origin as hyalinized and thickened vessels with narrowed lumina are seen everywhere. In addition, the larger arteries show atheromatous changes.

Thus angiospastic encephalopathy appears to be the most probable diagnosis.

#### Case 7.

Woman, aged 57, seamstress. Rec. No. III, 1687/43. Admitted 14/9—27/11/43.

Since 1935, mitral heart lesion and auricular fibrillation and functional dyspnea and precordial pain. In 1936, transitory paresis of the right arm, lasting a couple of days. 3 days before admission, unconsciousness lasting for several hours, without convulsions or paresis. The pupils were dilated, not reacting to light; and Babinski's sign + on both sides. Blood pressure: 270/170. No signs of cardiac insufficiency.

*Blood Pressure:* 210/140—180/95. *Electrocardiography:* Auricular fibrillation.

*Urine:* No albumin; + leucocytes; + colon bacilli. Urea clearance (maximum). 33 cm<sup>3</sup>. Diodrast clearance: 199 cm<sup>3</sup>.

*Ophthalmoscopy, 16/9:* Arteries markedly light-reflecting; + Gun's phenomenon; no hemorrhage or exudate.

*Spinal Fluid:* 17/9: Pressure 320 + increase in Queckenstedt's test; albumin 12; globulin 0; cells 0/3; Wassermann negative.

*Neurological Exam.,* 21/9: Slight accentuation of reflexes on right side. Babinski's sign doubtful on right side.

With a view to the pronounced angiospastic retinopathy, it is most likely that the cerebral phenomena are due to vascular spasms. Also the previous attack of transitory paresis is suggestive of this diagnosis.

#### Case 8.

Man, aged 52, yard master. Rec. No. III, 1763/43. Admitted 15/10—11/12/43.

For the last 18 months, headache. 2 weeks before admission, unconsciousness for 15 min. with spasms of the arms and legs. After this attack the patient was somewhat hazy, with lowering of the visual acuity. One hour later, a similar attack. Admitted to the Dep. of Neurology, from whence he was transferred to this Dep.

*Blood Pressure:* 210/130—175/100. *Electrocardiography:* Preponderance of the left side; T<sub>1</sub> diphasic.

*Urine:* + albumin; no pathological form-elements. Urea clearance (maximum): 67 cm<sup>2</sup>. Diodrast clearance: 295 cm<sup>2</sup>.

*Ophthalmoscopy:* Arteries markedly contracted; + Gun's phenomenon; + hemorrhage; + exudates. Paracentral scotomas on both sides.

*Spinal Fluid:* Pressure 390; + increase in Queckenstedt's test; albumin 11; globulin 0; cells 6/3; Wassermann negative.

*Neurological Exam.:* No abnormality.

#### Case 9.

Man, aged 57, mechanic. Rec. No. III, 149/44. Admitted 7/1—26/1/44.

In childhood, epilepsy; as adult, only 1 attack, at the age of 35. During last 7 years, periodical bronchitis.

On the day of admission, during work, sudden attack of paresis of the right arm; no unconsciousness, convulsions or disturbance of speech. After 2 hours, the paresis disappeared again quite suddenly.

*Blood Pressure,* on admission: 160/100; later: 140/70—120/65. *Electrocardiography:* No abnormality.

*Urine:* No albumin; no pathological form-elements. Urea clearance (maximum): 60 cm<sup>2</sup>. Diodrast clearance: 382 cm<sup>2</sup>.

*Ophthalmoscopy,* 11/1: No abnormality.

*Spinal Fluid,* 10/1: Pressure 220; + increase in Queckenstedt's test; albumin 20; globulin 0; cells 3/3; Wassermann negative.

*Neurological Exam.* 10/1: No abnormality.

#### Case 10.

Woman, aged 62, dental technician. Rec. No. III, 215/44. Admitted 15/12/43—11/2/44.

In December 1941 transitory impairment of vision, after which albu-



minuria and hypertension were ascertained. Later, increasing functional dyspnea, stenocardia, fatigue and headache. Lately, now and then, spasms of the arms and legs, and paresthesias of the left leg.

*Blood Pressure:* 220/130—170/100. *Electrocardiography:* Preponderance of the left side; T<sub>1</sub> negative.

*Urine:* + albumin. No pathological formed elements. Urea clearance (maximum): 6 cm<sup>3</sup>. Diodrast clearance: 34 cm<sup>3</sup>. Blood urea: 100—130 mg %. Serum bicarbonate: 43 vol. % CO<sub>2</sub>. Serum chloride: 338—355 mg %.

*Ophthalmoscopy:* Arteries contracted, silver-glistening; + exudate; + hemorrhage.

*Spinal Fluid:* Albumin 10; globulin 0; cells 0/3; Wassermann negative.

*Neurological Exam.:* Hyperesthesias of the left side and the abdomen and left lower extremity. Knee-jerks accentuated, but equal.

#### Case 11.

Man, aged 59, saddler. Rec. No. III, 335/44. Admitted 23/1—8/3/44.

In childhood, poliomyelitis with permanent impairment of the muscular power of the left lower extremity. During the past 10 years hypertension with dizziness and headache. On the day before admission, sudden paresis of the left arm and leg, together with aphasia and dyspnea. On admission, the pupils were dilated and reacting a little sluggishly to light. The symptoms subsided within a couple of hours after admission, but moderate difficulty in speaking and impairment of the muscular power persisted for nearly 4 weeks.

*Blood Pressure:* 280/160—230/130. *Electrocardiography:* Preponderance of the left side; all T waves negative.

*Urine:* + albumin; no pathological formed elements. Urea clearance (maximum): 27 cm<sup>3</sup>. Diodrast clearance: 188 cm<sup>3</sup>.

*Ophthalmoscopy,* 25/1: Vessels somewhat tortuous; + Gun's phenomenon; + exudate.

*Spinal fluid,* 24/1: Pressure 180; albumin 15; globulin 2; cells ½; Wassermann negative.

*Neurological Exam.,* 25/1: Impairment of muscular power of the left arm. Babinski's sign positive on the right side. Absence of reflexes in the left lower extremity (sequelæ of poliomyelitis).

#### Case 12.

Woman, aged 67, wife of workman. Rec. No. III, 397/44. Admitted 23/2—17/3/44.

For the past 3 years, functional dyspnea and palpitation of the heart; otherwise no signs of cardiac insufficiency. On the day of admission, while walking in the street, the patient suddenly had paralysis of the right lower extremity, a sensation of tightening round the mouth and paresthesias of the fingers; no convulsions, no unconsciousness. On admission to the hospital immediately after this attack, the paralysis had disappeared.

*Blood Pressure:* 190/100—130/80. On admission, auricular fibrillation. *Electrocardiography*, on the following day: No abnormality.

*Urine:* No albumin; no pathological formed elements. Urea standard clearance: 30 cm<sup>2</sup>.

*Ophthalmoscopy* 25/2: Vessels arteriosclerotic; no spasms. Chorioretinal atrophy with marked pigmentation.

*Spinal Fluid*, 24/2: Pressure 140; albumin 12, globulin 0; cells 0/3; Wassermann negative.

*Neurological Exam.*, 4/3: No definite abnormality.

Probably the patient is suffering from angiospastic encephalopathy as the symptoms are localized, whereas anoxia due to transitory auricular fibrillation presumably would give more diffuse intracranial symptoms.

#### Case 13.

Woman, aged 76, wife of painter. Rec. No. III, 871/44. Admitted 4/3—3/6/44.

For several years, headache and dizziness. Several times, transitory disturbance of speech — the last time about 1 year before admission when, the patient also had hemiplegia on the right side which subsided rapidly. Once her vision was impaired transitorily.

On the day of admission, brief spell of unconsciousness. On awakening emiplegia on the right side and aphasia. The disturbances of speech subsided in the course of the same day; the paralysis subsided slowly.

*Blood Pressure:* 220/120—165/70. *Electrocardiography*, on admission: normal findings; later: several transitory attacks of auricular fibrillation.

*Urine:* No albumin, no pathological formed elements. Urea standard clearance: 36 cm<sup>2</sup>.

*Ophthalmoscopy*, 27/3: Arteries thin, rigid; + Gun's phenomenon; no hemorrhage or exudate.

*Spinal Fluid*, 27/3: Pressure 140; + increase in Queckenstedt's test; albumin 15; globulin 0; cells 0/3, Wassermann negative.

*Neurological Exam.*, 28/3: Slight paresis and accentuation of reflexes on the right side.

Most likely the patient is suffering from angiospastic encephalopathy, as the symptoms kept being localized to the left hemisphere, whereas anoxia due to transitory auricular fibrillation would give more diffuse intracranial symptoms. Presumably the possibility of cerebral thrombosis can be excluded, as the attacks kept being elicited from the same vascular region through several years.

#### Case 14.

Man, aged 49, actor. Rec. No. III, 1045/44. Admitted 28/5—1/7/44.

Through the last 17 years intermittent claudication and attacks of "dead fingers". 3 weeks before admission, parasthesias of the left extremities, together with difficulty of speech that disappeared within a few days. 8 days before admission transitory blindness. On the day of admission, hemiplegia on the left side.

*Blood Pressure*, on adm.: 180/100; later: 145/80. *Electrocardiography*: Preponderance of the left side;  $T_1, 2, 3$ ; negative.

*Urine*: No albumin; no pathological formed elements. Urea clearance (maximum): 59 cm<sup>3</sup>.

*Ophthalmoscopy*, 31/5: Arteries thin; + Gun's phenomenon; + hemorrhage.

*Spinal fluid*, 29/5: Pressure 240; + increase in Queckenstedt's test; albumin 15; globulin 0; cells 0/3; Wassermann negative.

*Röntgenography* of the skull: Arteriosclerotic vessels on both sides of the sella turcica.

*Neurological Exam.*: Hemiplegia, left.

Presumably the symptoms presented by this patient are due to angiospastic encephalopathy complicated by cerebral thrombosis.

#### Case 15.

Woman, aged 56, shop assistant. Rec. No. III, 1271/44. Admitted 19/8—23/8/44.

For 10—15 years, hypertension with headache, dizziness and insomnia. 3—4 times, a brief fainting spell, with transitory slight pareses. Never convulsions or disturbances of speech.

On the day of admission, unconsciousness for 45 min., without pareses.

*Blood Pressure*: 220/130—195/115. *Electrocardiography*: Preponderance of the left side.

*Urine*: No albumin; + red blood cells; + casts; (+) leucocytes. Urea clearance (maximum): 59 cm<sup>3</sup>.

*Ophthalmoscopy*: No abnormality.

*Neurological Exam.*: No abnormality.

#### Case 16.

Woman, aged 68, old-age pensioner. Rec. III, No. 1421/44. Admitted 2/9—19/9/44.

For some length of time, loss of memory and insomnia. 7 months before admission, sudden blindness of the right eye. One week before admission, sudden attack of unconsciousness, lasting 15 min. Since then nausea, headache, dizziness and weakness of the left lower extremity.

*Blood Pressure*: 280/130—250/140. *Electrocardiography*: Preponderance of the left side.  $T_1, 2$  negative.

*Urine*: + albumin; no pathological formed elements. Urea clearance (maximum): 70 cm<sup>3</sup>.

*Ophthalmoscopy*, 5/9: Unequally calibrated, glistening, arteries; compression of veins here and there; thrombosis of the right central vein.

*Spinal Fluid*, 4/9: Pressure 160; + increase in Queckenstedt's test; albumin 18; globulin 1; cells 2/3; Wassermann negative.

*Neurological Exam.*, 5/9: No pareses; Babinski's sign positive on the left side; Achilles tendon reflexes absent.

Presumably the symptoms presented by the patient are due to angiospasm, as no manifest neurological symptoms are found outside the left Babinski's sign, but only the subjective impairment of muscular power.

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From the University Institute of Pathological Anatomy, Copenhagen  
Director: Professor J. Engelbreth-Holm M. D.

and

The Medical Clinic B., University of Copenhagen.  
Chief Physician: Professor Erik Warburg, M. D.

## Steatorrhoea arthro — pericarditica.

(Mesenteric chyladenectasis.)

Review and report of a case.

By

JOHANNES CLEMMESSEN.

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The object of the present paper is to call the attention of clinicians to a special form of steatorrhoea which hitherto has been recognised only at post mortem examinations, and consequently mainly dealt with by pathologists. As this kind of steatorrhoea mostly is associated with arthritic attacks and pericarditis, it is well characterised clinically, and it is the hope of the author that this review of ten cases now known, may facilitate the bed-side diagnosis as well as the pathological examination of future cases. No doubt these will be found more frequently than would be expected from the past.

Mesenteric chyladenectasis (Hill) which represents the main common feature of all reports reviewed in the following, is an excessive dilatation of the mesenteric lymph node sinuses caused by fat depositions and accompanied by infiltration of the neighbouring lymph node tissue by a varying number of lipophages, frequently in the shape of multinucleated giant cells. This latter histologic finding, named lipogranulomatosis, is not uncommon where disin-

tegrating fat is being absorbed, while, on the other hand chyladenectasis as such is considered extremely rare. With the exception of Kloos no author quotes more than a single earlier publication of such cases.

As mesenteric chyladenectasis has been the main criterion at the collection of the present reports, these form a selection of fatal cases within the strictest possible limitations. A thorough analysis of their clinical features is hampered by the schematic character of many clinical histories, found in pathological case reports. The most ample — and first — report was given in 1907 by Whipple whose case represents the most varied manifestations of the disease.

To complete the following list, it should be mentioned that in 1855 Rokitansky reported on similar postmortal findings but without referring to any histologic examination. In 1923 Blumgart communicated three fatal cases of malabsorption of fat. Comparing them with Whipple's case, Blumgart underlined the differences which also to a modern view would seem more outstanding than the similarities. Blumgart's second case may have developed a pathological picture similar to Whipple's, but unfortunately it has not been possible to decide this from the description at hand.

In 1938 the cases of Korsch and of Gaertner were discussed at a joint meeting of the German Pathological Society and Society for Intestinal and Metabolic Diseases. In the discussion Schultze referred to the case of a young man, who had been operated on and showed the same postmortal findings as the other patients, but no further clinical or pathological details were given. Also Beitzke had made a similar observation but »ich habe nicht recht gewusst was ich mit dem Befund anfangen sollte«.

As for the time being, all clinical and pathological details are indispensable for the judgement of such cases, the author has been unable to include those of Schultze and Beitzke in the following review. A report by Mohr 1939 has not been accessible to the author.

### Case reports.

#### I. Whipple's case. 1907.

Medical missionary, aged 36. Measles and whooping cough as a child. Chills and fever at 10. Slight attack of pleurisy at 14 — in bed only a day or so. (Pleurodynia? J. C.) 29 years old, attack of influenza.

For four and a half years expectoration of moderate quantity, and for five and a half years frequent, but transient attacks of arthritis, affecting nearly every joint. Sometimes the joints were hot, swollen and tender; at other times only painful. The attacks were never associated with fever and on but one occasion were they of sufficient severity to confine him to bed and for but two days. Gradually a notable loss of strength and weight developed, expectoration increased, and evening temperature rose to about 100 (37.8° C) nine months before death. Three months later a diarrhoea of steatorrhoic character set in. The appetite remained good, but a swelling of the abdomen increased. A palpable mass developed below and to the right of the umbilicus. Hypochromic anaemia and periodic eosinophilia, purpuric cutaneous spots, hot, swollen and discoloured ankles were observed in the hospital. Exploratory laparotomy was performed, and led to a diagnosis of Sarcoma or Hodgkin's disease of the mesenteric lymph nodes. The patient died rather suddenly a few days later.

10 days before death: Dried stool, 20 gms  $\left\{ \begin{array}{l} \text{Neutral fat, 10 gms.} \\ \text{Fatty acids, 6 gms.} \\ \text{Organic salts etc. 4 gms.} \end{array} \right.$

*Anatomical diagnosis:* — Neutral fat and fatty acid deposits in intestinal mucosa, mesenteric and retroperitoneal glands and thoracic duct; chronic lymphadenitis; anaemia; emaciation; organizing peritonitis, pleuritis, pericarditis and aortic endocarditis; cardiac dilatation and hypertrophy with fatty degeneration; chronic passive congestion of viscera; splenic tumor; hyperplasia of bone marrow; cloudy swelling of viscera; laparotomy wound; bronchopneumonia and oedema of lungs; caseous apical scar and tuberculous bronchial lymphadenitis.

## II. Fahr's case. 1928.

Male aged 44. No previous important disease. At 38 he suffered for six months from the effects of intoxication by cyanic nitroglycerin. He started working again, but never reached his full strength, and had troubles interpreted as schiatica and rheumatism.

Six months before death he became dyspnoeic with coughing and sometimes abundant expectoration. At this time he began suffering from diarrhoeas. Wassermann reaction was positive, but syphilis was denied. A finding of tubercle bacilli was never confirmed. Blood pressure was 95 mm. Hemoglobin was 35 %, Erythrocytes 2.4 Mill. Colour Index 0.46. There was a slight dullness at the apex, and some meteorism. There was never any increase of temperature.

Autopsy: 164 cm 46 kg.

Marked universal anaemia. Swelling of mesenteric, retroperitoneal and supraclavicular lymph nodes. Rather extensive old adhesions in all serous cavities (pleural and pericardial sacs, peritoneum.) Old tuberculous foci in the tracheobronchial and right pulmonary nodes. Slight universal arteriosclerosis. Oedema of wall of large intestine. Small ulcers of the



epiglottis and aryepiglottic plicae. (decubital ulcers.) Spleen 150 grammes, soft elastic, dark grey at the cut surface, where abundant very small whitish spots may be observed. Also in the enlarged lymph nodes there are grey-whitish spots of pin-head size. They are slightly similar to tubercles, but microscopical examination justifies no connection either with tubercles or other forms of granuloma.

Fahr described two sorts of changes in the lymph nodes: The nodes are infiltrated by numerous large and small round masses, consisting of confluent fat surrounded by numerous giant cells resembling foreign body giant cells. Furthermore there are numerous nests of fat-containing cells of reticular origin.

Nothing special was reported with regard to the histologic examination of the small intestine.

From the descriptions of Fahr's histologic findings and from his micrographs it seems certain to the author — as it did to Fahr himself — that this case represents a perfect analogy to the other cases produced at the meeting of the German pathological Society 1938, and it seems unjustified to exclude it from the list (Kloos).

### III. Fleischmann's case. 1930.

Male aged 38. For years suffering from «rheumatism of the joints». Eight months before death severe emaciation developed, followed by feelings of pressure and pain in the abdomen, and discharge of gas. Laparotomy showed enlarged lymphnodes, and a diagnosis of sarcoma was suspected. Temperature remained slightly increased, and death occurred one week after the operation.

Patho-anatomical diagnosis: Multiple foreign body granulomas of the mesentery, following fat necrosis. (after pancreatic necrosis?). Bronchopneumonias of both lower lobes, accompanied by catarrhal purulent tracheitis and bronchitis. Double sero-hæmorrhagic pleuritis.

Pericardial symphysis. Heart dilated with brown atrophy of myocard. Anæmia and progressive fatty infiltration of liver. Cloudy swelling of kidneys. Anæmia. Emaciation. Laparotomy wound.

### IV. Hill's case. 1937.

Polish farmer, aged 60. About four months before death epigastric pains, vomiting and diarrhoea. No history of any relative past illness could be obtained, with the exception of a similar attack 1 year previous. The latter assertion was made on only one occasion and could not be confirmed.

There was a moderate anemia (Hb. 60 %), a blood sugar of 35 mg %. The patient who was extremely emaciated subsequently became extremely weak, and hypotension developed. His appetite was good, but he was somnolent. The temperature never exceeded normal except during the period just before death. Mental confusion developed, then coma, and the patient died. «Postmortal findings: Chronic inflammation and fibrosis

in the lymph nodes of the entire mesenteric, peripancreatic and upper retroperitoneal regions.

The presence of Gram-positive cocci in chains in the lymphatic vessels and lymph nodes was demonstrated. Their number ran parallel with the degree of polymorphonuclear leukocytic infiltration. In the lower mesenteric nodes small numbers of these organisms were found, most frequently located in the perivascular lymph spaces.

Anatomical diagnoses: Mesenteric chyladenectasis, chronic and acute mesenteric and retroperitoneal lymphadenitis and lymphangitis, chronic pancreatitis with islet hyperplasia, moderate generalized arteriosclerosis, nephrosclerosis, brown atrophy of heart, chronic passive hyperemia of liver, spleen, and gastrointestinal tract, chronic fibrous adhesive pericarditis, hypostatic bronchopneumonia, and acute serofibrinous pleuritis.

(Presumably it is erroneous when stated by Glynn & Rosenheim that Hill's case was complicated with steatorrhea.)

#### V. Glynn & Rosenheim's case, 1937.

Male aged 44. Nothing in his past history to suggest any preceding abdominal lesions. 1 year before death upper abdominal pain. Constipation, loss of weight and strength and occult blood in the stools developed within a few months. After 6 months illness the total fats in the stools were 44.4 per cent. (neutral fats 5.6 per cent, soaps and fatty acids together 38.8 per cent.) After some time of relative improvement again he lost weight and was now febrile. Stools were copious, clay coloured and frothy. 1 month before death they contained 48 per cent of total fats (neutral fats 22 per cent, split fats 26 per cent.) His appetite remained good. At the end temperature was normal. Slight pigmentation, lassitude and low blood pressure, suggested Addison's disease, and there was favourable reaction to Eucortone, but diarrhoea recurred and he died.

(Author's extract from the autopsy statement):

Heart: 440 g enlarged, chronic fibroid pericarditis. Tardieu spots posteriorly, ventricles dilated and hypertrophied.

Lungs: extensive dry pleurisy on right side, patchy pneumonia of both lungs hilar and tracheo-bronchial glands large and fleshy and acutely inflamed, bloodstained muco-pus in air passages.

Liver: surface covered with sugar icing coating.

Spleen: — sugar icing coating.

Small intestine showed atrophy of the mucosa and Peyer's patches with marked thickening of the serous coat. Duodenum thick and of rubbery consistency. No ascites.

Lymph glands: All the mesenteric lymph glands were greatly enlarged varying in size from  $1 \times 0.5$  to  $3.5 \times 2$  cm the whole mass being approximately the size of a foetal head ( $17 \times 8 \times 4$  cm). — The afferent lymphatics were markedly dilated. There was no enlargement of the lymph glands of the groins, axillæ or neck, but those along the aorta and iliac arteries were slightly enlarged and there were a few very large glands projecting from the brim of the pelvis. — No evidence of obstruction in the thoracic

duct was found. The cisterna chyli and large abdominal lymph trunks were not examined. Small intestine: fat both in the villi and in the sub-mucous lymphatics. Many fat-filled macrophages were present in the sub-mucous tissues.

The diagnosis was of Mesenteric chyladenectasis with steatorrhoea and features of Addison's disease.

#### VI. Korsch's case. 1938.

Male aged 60. Measles as a child, later gonorrhoea. For ten years «rheumatic troubles». For one year expectoration, and weekly attacks of dizziness and perspiration. During the last nine months he lost 10 kg, the appetite diminished, epigastric pressure and vomiting developed. The stools passed irregularly but were of a normal colour. Later there was some epigastric tenderness on pressure. The temperature sometimes rose slightly. By radiography an extraventricular tumour was recognised. Mental confusion developed sub finem.

Patho-anatomical diagnosis: Lipogranulomatosis of the lymph vessels from the small intestine. Oil droplets in the chylus vessels of the villi. Lipogranulomatosis especially of mesenteric and retroperitoneal lymph nodes confluent to masses of fist-size but less pronounced in mediastinal and paratracheal lymph nodes.

Chronic verrucous endocarditis of aortic valves, without fusion. Former valvular mitral endocarditis with calcification. Slackness and dilatation of both ventricles. Open foramen ovale. Complete obliteration of pericardial cavity. Chronic pulmonary emphysema and oedema. Harder patches of esophageal mucosa. Slight diffuse colloid goiter. Recent congestion of liver with cloudy swelling. Splenic tumour with enlargement of Malpighian bodies. Right kidney small and deeply situated. Apparent compensatory hypertrophy of left kidney. Ureteritis Pyelitis and Cystitis cystica. Prostatic adenomyomatosis. Almost complete fatty degeneration of adrenal cortex. Scars and recent ulcers of the duodenum. Signs of old bleedings (pigmented spots) in duodenal mucosa.

#### VII. Gaertner's case. 1938.

Master butcher aged 30, whose father had suffered from rheumatism and heart failure.

No important diseases in the past, but for three or four years transient swelling of the wrists without material rise of temperature. One year before death a persistent diarrhoea set in, together with the loss of 28 kg in six months. The stools turned grey, and examinations revealed gastric achylia, and an increase of diastasis in the urine. (100 E., 600 E.). Following an improvement of some months, a hæmorrhagic diathesis developed, the blood pressure decreased, and temperature was below normal during the last few days.

Patho-anatomical findings: Chronic enteritis. Strongly pronounced deposition of fat in mesenteric lymph nodes. Bronchopneumonia.

Chronic enteritis of entire intestinal mucose with atrophy and dark mucosal pigmentation. Considerable enlargement of mesenteric lymph nodes through deposition of fat. Considerable anaemia and emaciation. Atrophy of epicardial and other fat tissues. Brown atrophy of heart. Hypoplasia of the aorta. Brown atrophy of liver. Bronchopneumonia of both lower lobes. Oedema of lungs. Recent pleuritis fibrinosa of both lower lobes. 200 cm<sup>3</sup> serous fluid in both pleural sacs. Small-spotted dark pigmentation of the peritoneal lining of the diaphragm and anterior abdominal wall. Oedema of both legs. Thrombosis of inferior vena cava and iliac pelvic and crural veins in beginning organisation.

It is stated that *Erhaltungszustand der Darmwand ist sehr schlecht*. Presumably this is the reason why no lipogranulomatosis of the intestinal wall was observed, in contrast to the other cases in which the patient had suffered from steatorrhoea.

#### VIII. Hansen & Staa—Jeckeln's case. 1936—1939.

Ernst N.

Male aged 55. No previous severe illness. No enteritis during war service. At 40 transient gastric troubles. At 49 rheumatic troubles. Three years before death, violent diarrhoeas following a year of interchanging diarrhoea and constipation. Some months later swelling of both ankles, and subsequently swelling, redness and bleeding of the gums. After another month there was an extensive subcutaneous bleeding on the left thigh. In three months time the patient had lost 15 kg, and was now admitted in hospital.

Height: 164.5 cm. Weight: 50.7 kg. There was a greyish-brown pigmentation with slight hyperkeratosis and desquamation of the neck, hands, dorsal of the feet, over the scapulae and the seat. There were numerous small hæmorrhages in the skin and subcutaneous tissues, and at the ankles as well.

In the report of this period Hansen & Staa give numerous laboratory results, a few of which will be quoted here:

Blood pressure was between 105/45 and 110/60. Electrocardiography and radiography of lungs gave normal results. Temperature was normal.

Stools were normal during the first days. Later he discharged 600 to 1200 grammes of typical sprue stools daily, in three to six times.

Urine was normal. Diastasis of the urine amounted to 16 units. There was a complete achylia. Calcium of the serum was 13 mg %. Blood examination showed anaemia (36 %) with a colour index of 0.9. Eosinophils amounted to 3 per cent. On application of Campolon there was a reticulocyte increase from 4 ‰ to 68 ‰ in the course of few days. Bleeding time measured 2 ½ minute. Coagulation time 4 ½ minute. Treatment with Vitamin C improved the hæmorrhagic tendency and the stomatitis, and he returned home.

Jeckeln (1939) reports some improvement with only occasional diarrhoeas, and a tendency to crural oedema in the following time. Then there was a relapse, and he was readmitted in hospital in Aug. 37 — a month

before his death. There was then oedema of the left leg. Stools were greyish with a film of mother-of-pearl on the surface. Hemoglobin amounted to 44 %, Erythrocytes to 3.3 Mill. Temperature was slightly elevated, 37.8 at the most, and in spite of different treatments there was loss of strength, and he died with pronounced symptoms of heart failure.

Jeckeln considers the case as a peculiar form of non-tropical sprue, and discusses the possibility of a complicating sepsis.

Post-mortal findings: Chronic mitral endocarditis with thickening and fusion of the chordæ, but without essential scar formation at the free valvular margin. Ulcerous and globular endocarditis of aortic valves with very considerable excrescences, mostly unorganised. Multiple scars of back wall of left ventricle, almost without any coronary sclerosis. Firm and slight splenic tumour with multiple anaemic infarctions. Nephritis of left kidney, failing development of the right. Brown induration and marginal emphysema of lungs. Chronic passive congestion of liver. Small mucosa scars in the duodenal bulb. A diverticulum-like sack about the size of a finger end in the juxtapyloric part of the duodenum. Peculiar mother-of-pearl — like shining deposits of fat in the mucosa of the small intestine with considerable oedema of the wall. Fat deposits causing firm swelling of mesenteric lymph nodes. Considerable emaciation, and universal palour. Brown atrophy of myocard with tigering. Hæmosiderosis of spleen. Small hæmorrhages of the pharynx wall. Subpleural hæmorrhages. Calcified focus in upper lobe of right lung and adhesions of pleura. Calcification of corresponding peribronchal lymph node. Slight universal arteriosclerosis.

On microscopical examination it was found that the villi had almost entirely disappeared, and were replaced by elevations presumably formed by confluence of villi. Instead of stroma was found a layer of bright cells with marked borders as in plant cells, and with a loose structure. Droplets of fat were also observed.

From the histologic descriptions and photomicrographs it seems most likely that the intestinal mucosa presented the same histologic features as in the author's own case. Of the mesenteric lymph nodes it is only stated that they showed a marked deposition of fat in the sinuses. Other histological changes seem to have been slight.

#### IX. Kloos's case. 1939.

Engineer aged 41. At 20 a swollen lymph node removed from the neck. At 32 appendectomy followed by angina.

18 months before death a three weeks' swelling of both wrists accompanied by tearing pains and followed by similar attacks of the knee joint and ankles. After a period of improvement, renewed attacks of pain without swelling.

During the last year loss of strength and appetite, and increasing pigmentation of face and hands. Stinging pains in the left thorax and expectoration of small quantity. Both ankles swollen and painful. There was a steady loss of weight.

At admittance in hospital. Height was 174 cm. Weight was 50.8 kg. The skin was dry with brownish colour of face and hands, but without pigmentation of oral mucosa. There were cutaneous hæmorrhages at the ankles, furthermore an ulcerous gingivitis, a chronic gastritis and duodenitis with achylia, refractory to histamine stimulation.

Blood pressure was 105/65. There was a hyperchromic anaemia (64 %) and temperature was slightly increased. Sedimentation rate was 13-65 mm. Coagulation time was 1 minute. The Rumpel-Leede phenomenon was negative. Diastasis of the urine was between 4 and 16. Serum albumin was 3.96, Nitrogen residual 56 mg per 100 cm<sup>3</sup>. Blood urea: 55 mg per 100 cm<sup>3</sup>. Blood sugar was 0.096 and NaCl 598 mg per 100 cm<sup>3</sup> after several infusions.

After a short time at home, swelling and burning of the ankles increased, and there was a complete loss of appetite. By different treatments anaemia was improved, and the values of serum proteins and NaCl returned to normal. He felt better for a short time, but temperature which at times had been high, remained so, and loss of appetite and weight continued. The stools had been irregular, and often pale. Now they were almost acholic, but formed. Abdominal pains developed, and the patient died.

The clinical diagnosis was of chronic gastroenteritis with disturbance of resorption, and acute liver cirrhosis, together with peritonitis causing paralytic ileus.

The summary of post-mortal findings:

Fatty infiltration of mucosa in upper small intestine, and the corresponding mesenterial and para-aortic lymph nodes. Emaciation and anaemia. Propagating purulent peritonitis. Fibrinous purulent pleuritis of right side, and adhesions over right apex. Fibrinous left pleuritis. Former mitral endocarditis. Fibrinous pericarditis with beginning pericardial concretion. Aspiration in both lungs. Sugar icing coating of liver and spleen. Brown atrophy of myocard. Old small subcutaneous bleedings on the left crus.

Kloos has given a review of five of the earlier cases here reported, and discussed different chemical possibilities, as well as fat analyses with great thoroughness.

X. Author's own case.

### Case Record.

Agricultural worker, aged 27.

No instance of hemorrhagic disease is known to have occurred in the family.

At the age of 15 years the patient had an attack of rheumatic fever for which he was treated at home with confinement to bed for one month; the symptoms consisted in pain in the right shoulder, accompanied by fever. There was no cardiac complication but later he was exempted from military service on the basis of a certificate concerning this attack. At the

age of 23—24 he had an attack of «nephritis» (macroscopic hematuria) for which he again was treated at home. No renal symptoms have appeared since.

In spring 1943 he had periodical attacks of a moderate swelling of the left knee, each period lasting a couple of days, but the tenderness of the knee was insignificant and the patient was able to attend to his work. From that point of time he commenced to lose a good deal in weight.

In the latter part of August 1943 — about 6 months before exitus — the patient noticed for the first time a sensation of cardiac oppression and indefinite epigastric pain, accompanied by a very persistent diarrhea, occasionally with an admixture of blood in the stools. The pain appeared 1—2 hours after the meals, but there was no rausea or vomiting. After about one month the patient had to keep his bed on account of tiredness, and a couple of weeks later — in the beginning of October 1943 — the physician ascertained the presence of blood in the stools and anemia. In spite of administration of vitamin C, bleeding from the gingivae appeared too and sometimes epistaxis several times daily. During his confinement to bed, with permission to get up and wash himself and use the W. C., the left ankle commenced to swell, and movements in the left hip became painful.

From the beginning of October 1943, when his lesion was diagnosed as peptic ulcer, the patient was treated with a diet of gruel and porridge. As the hemorrhage recurred, he was admitted to the Ringsted Hospital,<sup>1</sup> where he stayed from 29/11/43 to 8/2/44, when he was transferred to the Medical Department B of the Rigshospital, where he stayed till he died.

In the Ringsted Hospital the physical examination revealed swelling of the interdental papillae and remnant of hemorrhage. There was swelling of the left ankle round both malleoli, accumulation of fluid in the ankle-joint, and tenderness to pressure along the joint line. The dorsal flexion was slightly reduced, but the movements were free from pain, and at this point of time there was no suggilation, redness or local heat of the ankle. There was fluid in the knee joint on both sides, no other abnormalities were found on physical examination.

During his stay in the hospital the temperature was subfebrile but as a rule the evening temperature did not exceed 38°. Ewald test meal:

4/12: 80 + 39 cm<sup>3</sup>, poorly chymified; + mucous; free acid 0; total ac. 26  
6/12: 20 + 60 cm<sup>3</sup>, » » ++ » » » 0 » » 18

Feces: Benzedine reaction for blood positive.

Hemoglobin:	30/11	8/12	23/12	6/1	20/1	3/2
	58%	37%	50%	45%	45%	50%

Sedimentation

rate:	134	128	95	70	40	90 mm/hr
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Blood examination, 2/12:

<sup>1</sup> The authors thanks are due to Dr. F. K. Frederiksen, Chief-physician of the Ringsted Hospital for his permission to publish the case history.

Red blood cells: 2.7 mill. Hb. 55 %. Color index: 1.0. White blood cells 7800. Differential count: Segment-nuclear neutrophils: 68  $\frac{1}{2}$  %; staff-nuclears  $\frac{1}{2}$  %; eosinophils 13 %; basophils  $\frac{1}{2}$  %; lymphocytes 12  $\frac{1}{2}$  %; monocytes 4  $\frac{1}{2}$  %; plasma cells  $\frac{1}{2}$  %.

Red blood picture: Normal. Platelet count: 425,000 per mm<sup>3</sup>.

Bleeding time normal (2 min.)

Capillary resistance test, 70—80 mm, 15 min.: 80 petechiae.

Blood ascorbic acid: 0.22 mg %. Blood urea: 28 mg %.

Roentgenography of the gastro-intestinal tract; Lumbar column and pelvis showed no pathological changes.

Rectoscopy revealed a readily bleeding area on the anterior wall of the rectum, just inside the anus, but otherwise no abnormality.

Electrocardiography: No abnormality.

Blood pressure, on 30/11: 140/80; on 7/12: 120/70.

Urine: No abnormal elements; microscopic exam. on 30/11 and 8/12: No abnormality.

Wassermann negative. Widal negative. Mantoux negative.

Blood cultures: No growth.

The cultures from gastric lavage: No growth.

» » » urine and feces: No pathogenic intestinal bacteria.

*Diagnosis:* Hemorrhagic diathesis; Anemia, severe degree; Thrombasthenia?; Colitis; Gastric achylia.

*Treatment:* Blood transfusion was given on 10/12 and 31/12, 500 cm<sup>3</sup> of blood each time. In addition, the following remedies were prescribed:

23/12: Hepsol fortior, 1 cm<sup>3</sup> every other day. Pepsin hydrochloric acid, 5 cm<sup>3</sup>  $\times$  3 daily.

31/12: Compolon Bayer, 5 cm<sup>3</sup> every other day.

Besides, the patient was given local treatment for the gingival bleeding and the joint pain.

A couple of times the patient complained of pain in the throat, which was swollen and very tender. As also an accumulation of fluid in the knee-joint persisted, the patient received from

13/1: Vitamin K (Kvitasol), 10 mg every other day, and

20/1: Vitamin P (Citrimin), 4 cm<sup>3</sup> intravenously daily. Still the joint pains were rather increasing in intensity when the patient was transferred to the Rigshospital.

On admission to the Medical Department B of the Rigshospital, on 8/2/44, the patient complained chiefly of overwhelming tiredness and pains in the ankle. The dyspeptic complaints were insignificant after the patient had been placed on a purée diet without meat, from September 1943. He even stated that he did not feel really ill.

*Physical exam.:* The patient was found to be emaciated, anemic and rather exhausted. The pupils, tongue, tonsils, chest and abdomen showed no abnormality. The gingivae were swollen, intensely red and bleeding readily. The mucous membrane showed a few miliary bluish hemorrhages.



The dorsal surface of both hands presented now a good many bluish red petechiae, but otherwise no skin hemorrhages. The fingernails were arcuate, but, the patient stated, they had always been of that shape.

On palpation of the left hip, which was kept in outward rotation, there was a marked tenderness; the left ankle was markedly swollen, exceedingly tender to touch, with bluish discoloration. The right ankle-joint was swollen too and tender, but in a lesser degree. The knees were kept flexed. During the patient's stay in this department the following examinations were carried out:

*Blood examination:*

9/2: Red blood cells: 2.4 mill. Hb.: 40 %. Vol. %: 18. Color index: 0.82. Vol. index: 0.87.

Average diameter of red blood cells: 7.9  $\mu$ . (Diffractometry)

Platelet count: 282,000 per mm<sup>3</sup>.

White blood cells: 5500.

Segment-nuclear neutrophils: 54 %

Staff-nuclear » 13 %

Eosinophils: ..... 1 %

Lymphocytes: ..... 30 %

Monocytes: ..... 2 %

Red blood picture: Moderate anisocytosis and pessary forms.

17/2: Red blood cells: 1.6 mill. Hb.: 32 %. Vol. %: 15. Color index: 0.93. Vol. index: 1.06.

White blood cells: 4300

Segment-nuclear neutrophils 50 %

Staff-nuclear » 13 %

Eosinophils: ..... 3 %

Lymphocytes: ..... 34 %

Reticulocytes, 17/2: 5 %; 18/2: 3 %; 19/2: 2%; 21/2: 2%; 23/2: 1. ½ %.

*Sternal punctate:*

14/2: Cell count: 55,200. (200 cells counted)

Basophil erythroblasts ..... 4 %

Polychrom. » ..... 22 %

Orthochrom » ..... 4 %

Hemocytoblasts ..... ½ %

Neutrophil myelocytes ..... 17 %

» metamyelocytes .. 20 ½ %

» staff-nuclears .... 32 %

» segment-nuclears 14 ½ %

Immature eosinophils ..... 2 ½ %

Small lymphocytes ..... 11 %

Plasma cells ..... 2 %

Clotting time, 9/2: 2 ½ min. Bleeding time, 10/2: 3 ¼ min.

Capillary resistance test ad mod. Bexelius, 19/2: 2—3 petechiae.

*Blood chemistry:*

- 9/2: Blood ascorbic acid: 0.24 mg %.
- 24/2: Ascorbic acid tolerance test with 300 mg ascorbic acid.  
 Before inj. of ascorb. acid: 0.4 mg %  
 1 hour after inj. .... 0.4 »  
 2 hrs. » » ..... 0.6 »  
 3 » » » ..... 0.6 »  
 4 » » » ..... 0.56 »  
 5 » » » ..... 0.4 »
- 9/2: Blood urea: 35 mg %.
- 11/2: Specific gravity of serum: 1.0244. Serum protein (cale.): 6.2 mg %.  
 Kjeldahl: Serum protein, 5.9 mg %; serum albumin, 3.6 mg %.  
 Relative albumin percentage: 61.
- 14/2: Serum calcium, 9.3 mg %. Serum phosphorus, 3.8 mg %.  
 Serum chlorine, 95 milliequiv.  
 Total cations (Method: Christensen & Warburg) 14/2: 141; 17/2:  
 141.5; 28/2: 144.7 milliequiv.  
 Blood sugar, fasting, 1/3: 74 mg %; 2/3: 88 mg %; 3/3: 98 mg %;  
 4/3: 82 mg %.  
 Glucose tolerance test with 65 g glucose in 500 cm<sup>3</sup> water.  
 At 9.00 (fasting): 111 mg %.  
 » 9.15: 98      At 10.00: 158      At 10.45: 168  
 » 9.30: 114      » 10.15: 167      » 11.00: 162  
 » 9.45: 124      » 10.30: 158      » 11.15: 147
- Sedimentation rate, 9/2: 119 mm/hr; 22/2: 85 mm/hr.  
 Electrocardiogram: Normal. Galactose test, 11/2: No excretion.  
 Feces: Benzidin reaction for blood positive.  
 Urine: No albumin, blood, pus or sugar.
- 8/2: » + urobilinogen; 0 bile pigment.  
 Wassermann negative. Gonoreaction negative. Antistreptolysin  
 liter: 450.  
 Throat cultures, 1/3, 2/3, 3/3 and 3/4: No growth of hemolytic  
 streptococci.  
 Mantoux, strength I and III, 72 hours: Negative.

On 10/2 an attack of epistaxis appeared, and on the following day the stools were black. As steatorrhea was ascertained at the same time, meat was prescribed, together with liver extract (Hepsol fortior, 5 cm<sup>3</sup> daily) from 14/2 to 18/2. This, however, as well as transfusion of 500 cm<sup>3</sup> blood (Group 0) had no effect on the hemoglobin percentage, determined on capillary blood, which showed the following values:

12/2: 34 %; 17/2: 32 %; 21/2: 41 %; 25/2: 32 %; 3/3: 43 %.

The condition of the patient kept rather stationary — in spite of energetic and varying therapeutic measures:

- 16/2—6/3: Sodium chloride (up to 40 tablets daily) 0.25 g each.)  
 19/2—5/3: Pancreatic enzyme (Pancreon Rhenania), 3 tabl.  $\times$  3 d.  
 23/2—5/3: Inj. of desoxycorticosterone (Percorten Ciba), 5 mg intramuscularly.  
 10/2: Vitamin K (2-methyl-1.4-naphthohydroquinone disuccinate), 2 mg.  
 14/2: Vitamin K, 50 mg intravenously.

The unsatisfactory duration of the effect of this treatment will be evident from the following prothrombin values given in time values, expressed as percentages of the normal value: (arrows signify injections of vitamin K.)

9/2	10/2	↓	11/2	↓	16/2	17/2	18/2	19/2	21/2	23/2	25/2	28/2	1/3	4/3
49	72	↓	62	↓	76	104	87	67	55	57	55	56	56	53

In addition, the patient was given a culture of *Bac. acidophilus* and various analgetics.

During his stay in the hospital some improvement of the steatorrhea was noticed. The stools became light brownish, not fatglistening and less fetid. But the amount was still 486 g on 2/3, and 603 g on 3/3.

On 29/2 there was oedema of the feet and scrotum.

On 4/3, in the evening, again severe pain in both ankles, accompanied by swelling. On the following day, signs of pneumonia were ascertained on the left side (*pneumococcus* Type 18). Sulphathiazole was prescribed. While the temperature hitherto had been irregularly subfebrile (about 37° in the morning, 38° in the evening), it now rose to 39.9. The pulse rate rose to 140, the respiratory rate to 60.

The patient died on the following day.

*Autopsy*, 7/3 (The author).

Height: 169 cm. Weight: 62 kg. Nutrition poor.

The vertebral column was found to be straight, and the bonemarrow here was uniform, light red, without focal changes. The bonemarrow of the femur was homogeneous, firm, light greyish-red. The cortex of the femur was strikingly thick.

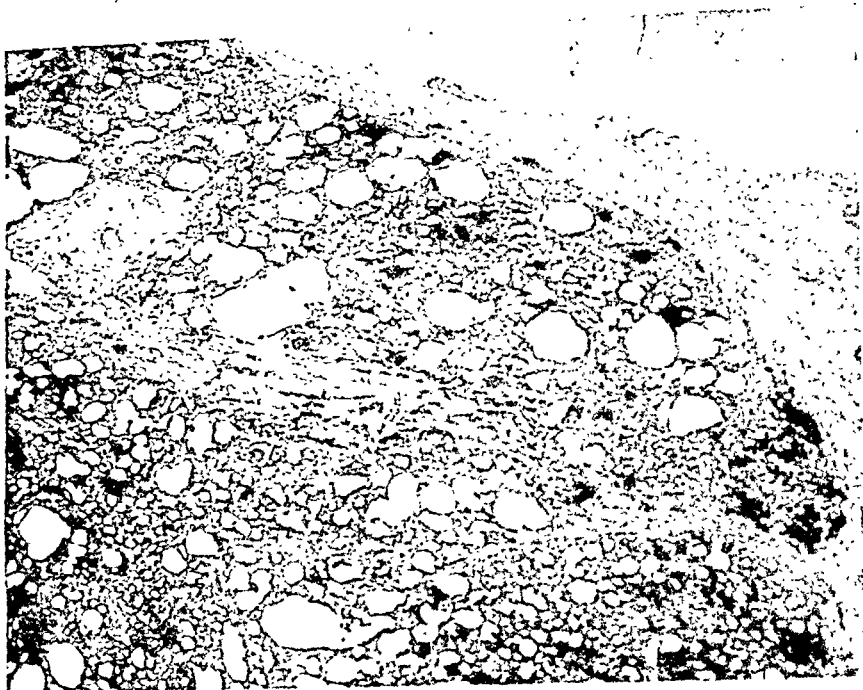
The neck organs appeared normal.

Pleurae smooth and glistening, without adhesions or patches of exudate. No fluid in the pleural cavity.

Lungs large, of normal form, uniform throughout, greyishred, somewhat lighter in color in the upper lobes anteriorly. On section, a considerable amount of oedematous fluid throughout, but no sign of pneumonia or other focal processes. Bronchi dry, without pathological changes. Hilar lymph nodes moderately enlarged, soft and uniform in consistency.

Pericardium without thickening or adhesions.

Heart normal in form and size; no changes in the endocardium and valves; myocardium of normal thickness, without focal processes. Coronary arteries, aorta and pulmonary artery normal. Esophagus normal. Peritoneum: Immediately after death formalin was injected into the peritoneal cavity; the intestines were well fixed, the stomach fairly well. The



I. Chyladenectatic lymph node.

fundus of the stomach was smooth, while the mucosal relief was well-pronounced in the pylorus. No ulcers were seen in the stomach or duodenum.

Throughout the intestinal canal the mucosal relief was well preserved, without constrictions, ulcers or tumors. Dimensions normal throughout. Clay-colored feces in the rectum.

The mesenteric lymph nodes were all moderately enlarged to a diameter of 1—3 cm. The nodes were well-defined, smooth, soft uniform and greyish-red on the cut surface.

Liver large, measuring  $33 \times 19 \times 10$  cm, but otherwise normal. Pancreas and adrenals normal.

Spleen normal in size and form, with semifluid pulp and effacement of pattern.

Kidneys pale, smooth, slightly enlarged, but otherwise without changes. Prostate normal.

Meninges and brain normal.

#### *Microscopic examination:*

*Lymph nodes* from the mesentery found to be studded with round cavities, measuring up to 1 mm in diameter; the tissue between these cavities showed a somewhat varying structure. In some areas the normal structure of the lymph node was preserved insofar as numerous lymphocytes were present, but in no place did these lymphocytes accumulate into a reaction focus. Other areas presented a varying number of lipophages,



II. Distended intestinal villi containing lipophages and a fat droplet.

which not infrequently had the form of giant-cells — especially at the margin of the cavities mentioned — and in some areas these cells had completely replaced the normal elements of the lymph node.

*Small intestine:* The mucous membrane was covered with very plump and broad villi, so that the intervals often were reduced to a narrow slit. The mucosa was well preserved, but the villi were quite filled with lipophages which had replaced all normal elements. Round cavities were seen only in a few places.

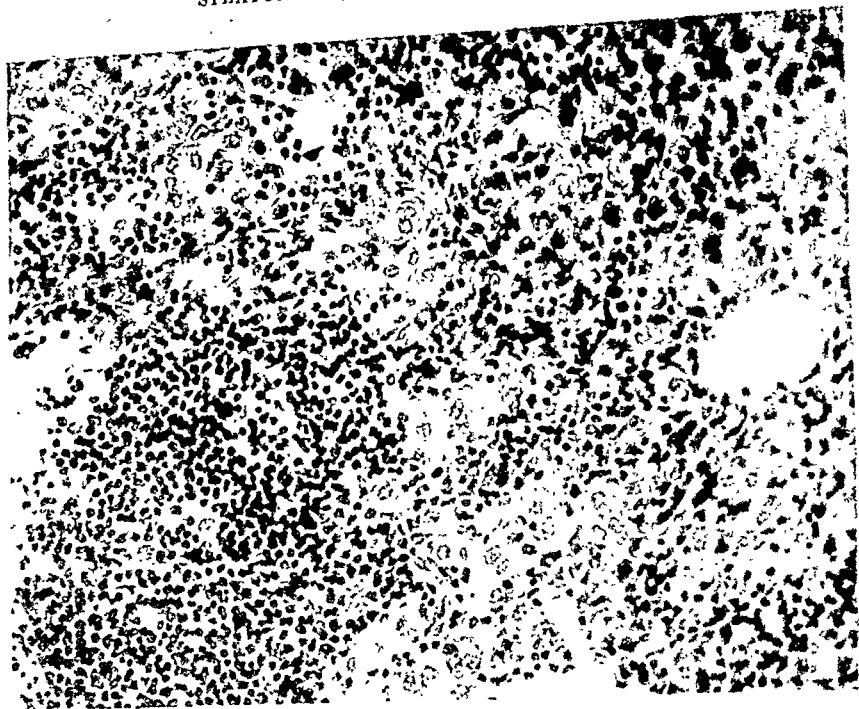
*Pylorus:* Mucous membrane well preserved, infiltrated with lymphocytes and a moderate number of plasma cells.

*Pancreas:* Islands of Langerhans well preserved.

By mistake, unfortunately, the organs were discarded, so that staining for fat and further examination of the lymphatic system could not be carried out. In the sections examined no Aschoff bodies or rheumatic affections of the vessels were observed.

*Autopsy diagnosis:* Mesenteric chyladenectasis with lipogranulomatosis; Lipogranulomatosis of the small intestines; Anemia of the organs; Oedema of the lungs; Acute hyperplasia of the spleen.

*Summary:* Agricultural worker, aged 27. At 15 rheumatic fever, showing itself as shoulder pains and increase of temperature. At 23 hæmaturia. Following six months' transient attacks of tender-



III. Lymph node infiltrated by lipophages.

ness and hyarthrosis of the knee joints, the present illness developed in the shape of tenacious, sometimes even hæmorrhagic diarrhoeas accompanied by painful and swollen joints suggesting intraarticular hæmorrhage.

In hospital steatorrhoea was demonstrated, together with deficiency in prothrombine rather refractory to injections of vitamin K, a rather low blood sugar curve, and a slight decrease of plasma protein. Other findings were: achylia, hypochromic anaemia, transient eosinophilia and lymphopenia. Blood sedimentation rate was increased, and temperature slightly elevated. There was a substantial increase of the antistreptolysin titre. The total amount of positive ions in the serum was decreased.

In spite of energetic and varied therapy, there was no improvement, and after six months' confinement to bed, the patient died with clinical signs of pneumonia.

Autopsy revealed mesenteric lymphnodes increased in size, and containing considerable deposits of fat. In the nodes as well as in the intestinal mucosa there was a very material infiltration of lipophages.

*Discussion:* Steatorrhoea which seems to be the most prominent clinical feature of the case has not been chemically verified. Nevertheless, as a diagnosis it is sufficiently well established, based on the appearance and considerable volume of the stools, and accompanied by hæmorrhagic tendency analogous to the hæmorrhagic tendency in cases of sprue, caused by insufficiency in absorption of fats. (Hult; Kark, Souter & Hayward; From Hansen & Begtrup.) Deficient fat absorption seems also the most probable explanation of the rather low blood sugar curve. (Krarup & Gortz).

As far as the last period is concerned, arthritic symptoms and slight elevation of temperature may have been caused by intra-articular hæmorrhage on the base of hæmorrhagic tendency. But as the patient had suffered from an attack of rheumatic fever twelve years previously, it is probable that the arthritic attacks inaugurating the final disease may have some connection with the old. Thus it may be significant that the antistreptolysin titre was elevated.

Transient eosinophilia was also present in Whipple's case whereas achylia was observed by Gaertner, by Jeckeln and by Kloos. It is true that Glynn & Rosenheim's patient had no achylia, so that these may be accidental findings.

*Clinical picture:* The diagnoses of the cases quoted above have been made post-mortem, based on microscopical examinations of mesenteric lymph nodes, which revealed dilatations of the sinuses caused by deposition of fat, and accompanied by infiltration of varying numbers of lipophages. In some cases, suffering from steatorrhoea, the intestinal villi were also infiltrated by these cells (I, V, VIII, IX ?, X).

Thus collected on purely patho-anatomical criteria, the different clinical case histories and autopsy protocols present so many features in common, that an attempted synthesis of a clinical picture seems justified. It follows as a matter of course that the application of this picture may reveal cases with identical pathological findings and a common pathogenesis but different with regard to etiological or symptomatic findings.

The present syndrome has hitherto been demonstrated exclusively in males. Almost all of them had for years before the appearance of more serious symptoms been suffering from transient arthritic attacks of a short duration. In most cases these attacks

have been described rather fragmentarily, but as a rule they seem to be localised to different joints. They are often followed by a slight rise of temperature, but they do not seem to have prevented the patients from working.

At the beginning of the last year of life the patients begin to loose weight, usually in spite of a good appetite. At about the same time epigastric pressure sets in, and after about six months a diarrhoea develops often followed by steatorrhoea. At this stage, the course of the disease is not infrequently interrupted by several months of improvement, but gradually a hæmorrhagic tendency develops, presumably due to deficiency in the resorption of vitamin K. It is not unlikely that a low blood sugar curve, as in the author's case, will prove common to all such patients.

Towards the end of the disease, which always has been fatal, a tumour consisting of conglomerates of enlarged lymph nodes may be palpable in the top of the abdomen. This finding may cause the undertaking of a laparotomy under a diagnosis of sarcoma, Hodgkin's disease or tuberculosis of the mesenteric lymph nodes. After some time of extreme weakness, a bronchopneumonia develops as the most common immediate cause of death. Psychotic disturbances may be observed during the last days.

*Diagnosis:* If the diagnosis of a disease has been made exclusively by autopsy, the question arises, how frequently this disease may occur and heal under another diagnosis.

In case of steatorrhoea, patients suffering from the present syndrome will as a rule pass under a diagnosis of non-tropical sprue. The infrequency of this latter diagnosis, makes it rather unlikely that «arthropericarditic steatorrhoea» should occur as a curable disease in numbers of any significance, though some cases may be pigeon-holed as pancreatitis or duodeno-colic fistula.

Among a number of reports of non-tropical sprue, given in the bibliography the author has found only two cases that may suggest a diagnosis of arthro-pericarditic steatorrhoea. The first case shows the strongest similarity with the authors own, and was published by Jeckeln as no. II, but the postmortal findings did not present any of the features, characteristic for the present syndrome. As it might represent a «missing link» between nontropical sprue, and arthro-pericarditic steatorrhoea, the following summary is given.



## Jeckeln's case-II 1939.

Merchant aged 32. As a youngster angina followed by polyarthritis and later swelling of the feet. During eighteen months increasing diarrhoeas, loss of strength and weight and subsequently development of hæmorrhagic tendency.

A laparotomy was performed to decide between a diagnosis of sprue and duodeno-colical fistula. No fistula was found, and some days later the patient died from a pneumonia.

The intestine was very cadaverous at autopsy, and the wall was very thin with some hæmorrhages. There was a medium melanosis coli, and a slight round cell infiltration in the mucosa of the small intestine. There was a chalky mesenterial lymph node about the size of a cherry, and the fat of the adrenals had diminished. The lungs showed different pneumonic changes, and a fibrosis of the right pleura, but there is no report of any of the pathological changes, characteristic of the cases earlier quoted.

## Müller's case 1937.

Male aged 41. Morbilli at 3. Since then of a very small stature. Twelve years old a paratyfoid fever, and at eighteen a so-called rheumatic fever with stiffness and pains in fingers and legs. He was treated at home for three weeks, and the doctor is reported to have characterised the disease as seldom. Since then, considerable deformities of the legs developed, and there has been periods of rheumatism with stiffness and pains, mainly in the finger joints, less in the feet.

At twenty-eight periods with loose and slimy stools, and discharge of gas. At thirty transient visual disturbances. At forty-one admitted in hospital for tetany. There was a tetany with deficiency of calcium and phosphorus, growth disturbances of the skeleton, prolonged Q-R-S-T, dyspepsia and steatorrhoea, slight hypochromic anaemia, and absence of hyperglykemia after ingestion of glucose. No achylia.

When Müller reported on the case, the patient was under treatment for intestinal hæmorrhage.

Müller's case may show patho-anatomical findings analogous to those found in the ten cases earlier reported, but the diagnosis will have to be kept in suspension, in the absence of any demonstration of pericardial or lymph node changes.

Generally it may be said that steatorrhoea and arthritic attacks combined with pericardial fibrosis, form the necessary base of a clinical diagnosis of steatorrhoea arthro-pericarditica. A biopsy of mesenteric lymph nodes, as in Korsch's case may alone lead to the diagnosis. In case of increased antistreptolysin titre, chemotherapy should be attempted. The reasons for this suggestion will be evident from the following pages.

*Pathogenesis.*

All authors on the subject, with the exception of Fleischmann whose perception of his own case as fat necrosis is shared by nobody, agree that the lymph node changes are due to the deposition of fat from the chylus. Glynn & Rosenheim have strongly supported this opinion by means of injection experiments and examinations of serial sections which showed that the ectatic cavities containing the fat deposits open directly to the lymph node sinuses.

Two theories — a chemical and a mechanical one — have been emitted to explain the pathogenesis of this deposition of fat.

The chemical explanation, supported more or less by Whipple, Korsch, Gaertner, Kloos, assumes a functional change of the pancreas or the adrenals as the cause of some anomaly in the synthesis of fats taking place in the intestinal mucosa. Consequently the fats of the chylus are supposed to be either physically or chemically abnormal, and so this »entartete Fett» (Korsch) is arrested in the mesenteric lymph nodes. (Korsch, Gaertner).

The foundation stones of this theory are to be found on somewhat scattered points.

Korsch has founded his opinion on the results of stainings by the Nile-blue sulphate and Smith-Dietrich methods, and Gaertner's argument is the size of the fat droplets. Furthermore Korsch considers the giant cells a foreign body reaction, speaking in favour of the theory of abnormal fats. These multinucleated lipophages may, however, be provoked at any decay of fats, nay they may even occur in subcutaneous fat depots in the absence of extracellular fat discernable by histological methods. (Koster & Behr). In fact, Kloos quotes a case of carcinoma of the gullet which caused a slowly progressing but incomplete blockage of the chylus stream in the thoracic duct, followed by infiltration of fats and phagocytes in the jejunal mesentery which turned stiff and tuberos. Thus it seems that merely a strongly pronounced slowing down of the chylus stream, presumably followed by disintegration of chylus fats may suffice to provoke the lipophages. Still it must be remembered that no infiltration by lipophages of the mesenteric lymph nodes or intestinal mucosa have been reported in any of the cases of »symptomatic sprue», referred to by the present author. These cases of

sprue were caused by Hodgkin's disease, sarcomata or tuberculosis of the mesentery, and the reason why no lipophages have been reported may partially be that destructive changes in the intestinal mucosa itself have played a pathogenetic part equal in importance to the lymphatic obstruction. Other factors as the speed with which the blockage develops may also be decisive, and finally it should be stressed that in many of the cases the intestinal wall has not been examined histologically.

As to the possibility of pathological changes in the functions of the pancreas, functional tests as determination of diastasis in urine, blood sugar curve, or nitrogen analysis of faeces, have not been reported sufficiently often to afford conclusive evidence, and the histological findings from the pancreas seem to be rather diverging. On the other hand, secondary pathological changes of this organ would easily be explained by the mechanical theory.

Glynn & Rosenheim have suggested functional disturbances of the adrenals in connection with the Addisonian symptoms observed in their case. Kloos has pointed to his own demonstration of scarcity in fats of the adrenals, and Korsch found an almost complete fatty degeneration of the adrenal cortex. Still the possibility of secondary adrenal changes seems to be very near at hand when metabolism is switched from fats to carbohydrate as the main source of energy, not to mention the retroperitoneal lymphatic inflammations supposed by the mechanical theory.

Finally it seems to be another weak point of the chemical theory that the pathological fats which are supposed to provoke a foreign body reaction of lipophages, do not succeed in this until they reach the lymph nodes. This must be the consequence of the fact that Korsch's case showed lipophages infiltrating the lymph nodes, while the intestinal mucosa remained normal. Already Whipple has pointed out that as scar tissue is more abundant in the lymph nodes than in the intestinal mucosa, it is probable that lipogranulomatosis is primary in the first place. The infiltration of the intestinal mucosa by lipophages, observed in most cases, must then be considered as secondary to the block in the nodes. It seems in conformity with this view that no report speaks of lipophages of the intestinal wall without changes of the lymph nodes.

The mechanical perception of the pathogenesis of the present syndrome was advanced by Hill, who succeeded in demonstrating

chronical inflammation and fibrosis of the mesenteric, pancreatic and upper retroperitoneal lymph nodes. There were also histological signs of chronic and acute inflammation of the lymph vessels with infiltration by polynuclear leucoocytes, and both in the lymph vessels, and the lower mesenteric nodes Gram-positive cocci in chains in numbers corresponding to the cell infiltration.

Hill believed that obstruction of large lymph trunks or the thoracic duct had caused the disease of his patient, and Glynn & Rosenheim were inclined to a similar view. It might now be advantageous to regard all the cases now known in the light of this theory.

It would seem a reasonable demand to any pathogenetic theory that it explain the occurrence of fibrous pericarditis in seven of the ten cases quoted above. Among these, five at least showed pericardial symphysis. In one of the two remaining cases an attack of rheumatic fever was reported twelve years before death (X) and the other patient was suffering from frequent rheumatic attacks accompanied by swelling of the wrists. (III)

Moreover, it deserves attention that eight of the clinical histories contain reports of arthritic attacks as the first manifestation of the disease. (I, II, III, VI, VII, VIII, IX, X) So these attacks cannot be explained as merely analogous to arthritic attacks observed in the later stages of non-tropical sprue. (Thaysen). The two remaining case reports are very scanty as far as the previous history is concerned, and the possibility of similar attacks in these cases cannot be excluded.

It is not without significance that four cases of pericardial symphysis (I, VI, VIII, IX.) were complicated with endocarditic changes. In two cases (I, II) peritoneum was the seat of fibrous changes, in two others (V, IX) of a hyaloseritis. The pleural sac had been affected in seven cases (I, II, III, IV, V, VII, IX), and in three of these it contained fluid. (III, IV, VII.) In this connection it must be noted, that bronchopneumonias which seem to be the most frequent cause of death, were found in six cases.

As the cause of this combination of arthritic attacks and pericarditis, not infrequently accompanied by endocarditic changes, together with a tendency of "polyserositis", it would seem natural to assume a rheumatic infection. It seems near at hand to expect

Table

Case no.	Author and year	Age and sex	Previous history	Rheumatic attacks	Steatorrhea	Hæmorrhagic diathesis
I.	Whipple 1907	M. 36	Expectoration 4 ½ yrs. 1 yr slight fever, loss of weight and strength. Increased abd. circumf. Swell. of lymph glands	5 ½ y.	6 months	cutaneous
II.	Fahr 1928	M. 44	Schiatica + rheumatism for 6 y. 6 months dyspnoe and expectoration	6 y.	no statement.	no statement
III.	Fleischmann 1930	M. 38	6 months' loss of weight. Abd. pressure	for years	no statement	no statement
IV.	Hill 1937	M. 60	Perhaps similar attacks 1 y. previously	no statement.	no statement.	no statement
V.	Glynn & Rosenheim 1937	M. 44	no statement	no statement	6 months	occult blood in stools
VI.	Korsch 1938	M. 60	Expectoration 1 y. Sweat and dizziness. Loss of weight and appetite. Epigastric pressure	10 y.	none	?
VII.	Gaertner 1938.	M. 30	Diarrhoea 1 y. Loss of weight and strength	3—4 y.	6 months anyhow.	cutaneous.
VIII.	Hansen-Staa-Jeckeln 1939	M. 55	«Rheumatic troubles» at 49. Diarrhoeas 3 y. before death	6 y.	first time 18 months ago	cutaneous subcutan
IX.	Kloos 1939	M. 41	18 months arthritic attacks. 1 y. loss of strength and weight. Pigmentations	18 months	periodically paler than norm.	surrounding the ankles
X.	Clemmesen 1945	M. 27	Rheumatic fever at 15. Hæmaturia at 23	6 months	6 months	cutaneous, in joints, in stools

Secondary findings	Clinical Diagnosis	Postmortal findings				Theory
		Chyla- denectasis	Lipo- granul. intest.	Peri- cardial fibros.	Endo- carditis	
	Mesenteric Sarcoma or Lymphogranulomatosis	+	+	+	aortic	Obscure disease of fat metabolism
WR: +		+	no statement	+		
Alveolar pyorrhoea	Mesenteric Sarcoma	+	0	+	0	Lipoid necrosis
Confusion	?	+	0	+	0	Lymphangitis. Sep rate group of mesent. cysts.
Normal Diastasis	Tub. peritonitis. Addison's d.	+	+	+	0	Lymphatic obstruction. Suprarenal insufficiency
Confusion	pancreatic Carcinoma	+	0	+	aortic and mitral	Chemical alteration of absorbed fat
Increased Diastasis	Pancreatitis	+	intest. mucosa cadaverous	0	0	Physical alteration of absorbed fat
Achylia Normal diastasis	Nontropical sprue. Anaemia. Scorbut. Osteoporosis	(+) (no lipo-gran.mes. reported.)	+	0	aortic and mitral	Peculiar nontropical sprue complicated by sepsis
Alveolar pyorrhoea. Achylia	Chron. gastroenterit. with disturbed resorption	+	+ ?	+	moderate shrinking of mitrals	Peculiar disturbance of fat resorption
Avitamin.-K.	Sprue nontropical	+	+	0	0	Pararheumatic infection

that affections of the pleural or pericardial sacs, or the joint cavities will be inclined to attack the large lymph trunks, whether by bacterial sepsis, or propagation, or as part of a general allergic reaction.

Hill's observations suggest that a lymphangitis caused by streptococci may be the cause of lymphatic obstruction in the mesentery. The rheumatic character of the clinical and pathological picture seems to be in full accordance with this assumption. Pericardial symphysis may be the cause of the hyaloseritis observed by Glynn & Rosenheim, (de la Chapelle & Graff, Bolton & Barnard, Siegert) and though an increase of the venous pressure it may also favour a partial lymphatic obstruction in the chylus system.

The following case, published by Ehrström in 1909, deserves attention as an example of steatorrhoea caused by mesenteric Lymphangitis.

*Ehrström's case. 1909.*

Architect, aged 45. Twelve years previously a rash in the face, followed by continuous development of carbuncles on back of the neck through four months. At the development and operation of an anal fistula, the carbuncles ceased to appear, but the stools turned more fluid and irregular.

Two years before death an apoplectic stroke, followed by transient monoplegia and aphasia. Later partially restored.

Eight months before death, bowels were moving regularly, but a few months later diarrhoea set in. Steatorrhoea was observed two months before death. The temperature was irregular, slightly increased, and the abdomen contained peculiar, tender tumours of varying localisation.

Autopsy revealed two emollitions in the brain. There is no special record of pericardial findings. Both pleural cavities contained fluid and the visceral blades showed fresh coverings of fibrin. Pneumonias were found in both lungs.

The mesentery of the small intestine had thickened considerably, forming a firm tumour, which on its surface presented numerous nodules the largest of which were about the size of a walnut.

Microscopical examination: The walls of the chylus vessels were thickened, infiltrated with small cells, and rich in connective tissue. The lymph nodes were replaced with ectatic cavities, partially or entirely surrounded with lymphatic tissue.

The lymphatic vessels nearest to the mesenteric radix were the seat of the heaviest cellular infiltration, and passed gradually into strings filled with detritus. All vessels in the radix itself had been completely obliterated.

The structure of the pancreas was normal, except for a small peripheral zone nearest to the mesentery, where a few necrotic foci were found together with an increase of fibrous tissue and a moderate infiltration of small cells.

The intestinal wall showed no changes.

Ehrström underlines the coincidence of acute and chronic inflammatory processes, and suggests their connection with the past furunculosis twelve years earlier.

In spite of the absence of typical chyladenectasis with lipogranulomatosis and pericarditis, preceded by arthritic attacks, Ehrström's case is still of interest in providing a close parallel to the pathogenesis suggested by Hill; in fact, the patho-anatomical differences between the cases of Hill and Ehrström may be ascribed to differences between the invading bacteria, or perhaps in their speed of invasion.

In Ehrström's case the lymph nodes seem to have developed very far towards mesenteric cysts, which — together with chylous ascites — is considered the most important consequences of lymphatic obstruction in the chylus system. The conditions under which these phenomena are replaced by chyladenectasis with lipogranulomatosis are still undefined, but it does seem a justifiable suggestion that a protracted slowing down, or a partial obstruction of the chylus flow will provide the circumstances most favorable to their development.

In summing up the pathogenetic considerations of this paper we are then justified in assuming the existence of a disease of parareumatic character, provoked by streptococci and causing inflammations of joints, serous cavities and mesenteric lymph vessels, which in their turn may produce mesenteric chyladenectasis and steatorrhoea.

The roles played by septic spread and allergic reactions are still difficult to evaluate. It is not unlikely that similar autopsy findings may develop on the base of other infections with similar localisation, and at present we cannot rule out the possibility, that the syndrome dealt with may represent a form or a phase of other sprue-like diseases.

The only way to increase our knowledge of this disease is thorough examination of all suspicious cases. These are likely to occur under the diagnoses of non-tropical sprue, abdominal tumour



or pancreatitis etc. So chymography of the heart, and biopsy of mesenteric lymph nodes may sometimes prove to be diagnostic auxiliaries of the same importance as functional pancreatic tests or analyses of the stools. Determination of the antistreptolysin titre would seem of interest as mesenteric lymphangitis might be just as accesible to chemotherapy as other erysipeloid infections, and parenteral administration of Vitamin K should also be tried in an early stage.

### Summary.

A review of nine cases, collected mainly from the patho-anatomical litterature, and a case report. The syndrome dealt with, comprises excessive dilatation of the mesenteric lymph node spaces caused by fat deposits. A fibrous pericarditis is also a frequent post-mortal finding. Clinically the disease begins with arthritic attacks, which after some years are followed by diarrhoeas, subsequently emaciation, and steatorrhoea, causing bleedings and finally bronchopneumonias. The author generalises the suggestion made by Hill, that the lymph node changes may develop on the base of a streptococcal lymphangitis of the mesentery, though other inflammations may have similar effects, if they provoke a partial lymphatic obstruction. It remains to be seen, whether septic spread or allergic reactions is the cause of arthritic attacks and pericarditis.

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(From the Department of Medicine, Sundby Hospital, Copenhagen. (Senior Physician: Professor H. C. Gram, M. D.)

## The Antistreptolysin Titer in Glomerular Nephritis.

By

KNUD LUNDBÆK.

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The determination of the antistreptolysin titer (AST) in nephritis is of importance for two reasons. First, it can give information about the etiology of the disease, secondly it might possibly be used for diagnostic purposes, especially in the differential diagnosis of different stages of glomerular nephritis.

Though it is now generally recognized that the hemolytic streptococcus is in an etiologic connection with most cases of acute nephritis (Longcope et al., 1927, Winkenwerder et al., 1935) it is still a point at issue *how* great the frequency of cases of nephritis due to pneumococci, non-hemolytic streptococci, pathogenetic intestinal bacteria etc. must be supposed to be.

It would be of the greatest importance to the — in some cases difficult — differential diagnosis between acute and chronic glomerular nephritis if the results of an AST-determination could be said to be of some value.

In the literature only 3 examinations of the AST in renal disorders seem to be reported. The first is by Longcope (1936). He finds unquestionable increase of the AST ( $\geq 200$ ) in 42 per cent. of 36 cases of acute nephritis, while only 3 per cent. of 31 cases of quiescent or chronic cases show increased values. — The second

material was published by Lyttle et al. (1938). It comprises chiefly children. In contradistinction to Longcope this investigator finds an increased AST in by far the greatest number of cases of acute nephritis, viz. in about 90 per cent. of 116 cases. — In his thesis (1942) Kalbak communicates 17 cases of AST-determinations in acute and chronic glomerular nephritis. In 3 cases of scarlatinal nephritis and in 10 cases of acute nephritis after other infections the AST was  $> 200$  in all cases. In 4 pts. with chronic nephritis values  $< 200$  were found.

The results of AST-determinations in a total of 106 pts. with acute and chronic glomerular nephritis will be communicated in the present publication. To obtain as great a material as possible I have included a number of cases of scarlatinal nephritis from the «Blegdamshospital» and a number of pts. who have been admitted to the Wards II, III, and VII of the Municipal Hospital and the Ward B and C of the Bispebjerg Hospital.<sup>1</sup> I endeavoured to get as many AST-determinations as possible in each patient in order to get an impression of the course of the AST-curve and the possible relation to the course of the disease. Of acute cases only pts. in whom more than one determination was made are included.

Only pts. in whom the diagnosis seems to be safe according to the current criteria are included. In pts. over 40 years the presence of a recognized acute infection within 5 weeks before the onset of the nephritis was considered necessary to accept the disorder as an acute one. As far as possible focal nephritis was excluded by the omission of pts. whose renal disorder developed in close connection with the infection, unless increased blood-pressure, decrease of renal function or passing into the chronic stage occurred. The cases of chronic glomerular nephritis were pts. whose renal disorder had been recognized several years before, or old pts. in whom routine examination revealed signs of chronic renal disorder. Probably a certain number of cases of nephrosclerosis is found in the latter group, but in the present material no attempt has been made to carry through the subtle, and most frequently impracticable, clinical differentiation between this condition and «genuine chronic glomerular nephritis».

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<sup>1</sup> My sincere thanks are due to the senior physicians of these wards for the material and the permission to use the case records of the wards.

## Results.

The tables show the results of the AST-determinations in scarlatinal nephritis, »other cases of acute nephritis» and chronic nephritis. In the columns marked »T», »Prot», and »Hemat». are stated the interval between the preceding infection and the onset of the nephritis, the duration of the proteinuria, and the duration of the hematuria — all of it in weeks. — In most cases the AST was determined once a week approximately. Omission of one or a couple of weekly determinations is shown by —, and omission of AST-determinations for any length of time by a parenthesis stating the duration of that period. In the case of scarlatinal nephritis the determinations begin on admission for the scarlatina. — In the case of »other cases of acute nephritis» the nature of the preceding infection, if known, is stated in a special column. It should be noted that tonsillitis acuta (Tons.) is most frequently an anamnestic diagnosis meaning angina faucium + fever.

It will appear from the table that by far most cases of acute nephritis have had an increased AST. The absolute values have been highly varying from one individual to another, ranging from < 200 to 8000 in scarlatinal nephritis, to 3200 in »other cases of nephritis». Extremely high values seem to occur somewhat more frequently in scarlatinal nephritis than in »other cases of nephritis», and in both groups doubtless more frequently in children than in adults. This may be due to the more frequent occurrence of complications in scarlatina, especially in children. (Lytle et al., 1938). It will, however, be seen from cases No. 28 and 25 that complications are not always associated with a very high AST and reversely. In No. 28 a value of 5000 was found at once and the AST remained over 2000 for 6 weeks despite an uncomplicated course. In No. 25 there was both otitis media suppurativa and ostitis ossis temporalis; but the AST was 110 at the utmost. In the former case the nephritis was serious with long-standing proteinuria and hematuria, in the latter case it was quite mild.

Only 6 pts. did not at any time display AST-values > 200, viz. 2 cases of scarlatinal nephritis and 4 of the group »other cases of acute nephritis».

Table 1.  
Scarlatinal Nephritis.

Nr.	Name	Case Nr.	Age	T.	Prot.	Hemat.	AST	Remarks
1	AH	2072/43	22	3	> 3	> 3	320. —, 320. —, 360.	Adenitis colli
2	EL	2264/43	22	2	÷	> 6	130. —, 230.	
3	AP	2547/43	6	3	1	> 6	910. —, 1440. 1280. —, 1280. 1150. 1025. 510. 800.	
4	KS	3218/43	22	3	÷	2	—, 160. 360.	Otitis med. supp.
5	RP	3434/43	6	1	÷	10	—, —, —, 1400. —, —, 640.	Adenitis colli
6	PR	3437/43	5	3	÷	4	250. —, —, 640. 640.	
7	BN	3496/43	8	2	÷	5	—, 720. 720. 575. 400. 250. 400. 320.	Adenitis colli
8	VL	3772/43	7	2	1	> 12	8000. —, 5000. 3200. 4500. —, 4000. 4000. 2800.	Adenitis colli
9	LN	4644/43	4	2	1	> 20	450. —, 720. —, —, 700. —, —, 200. (1 mth).	
10	AN	4658/43	7	2	÷	12	110. —, 160. 200. 250. 280.	Adenitis colli
11	CO	4734/43	5	2	> 1	3	3200. 8000.	Otitis med. cat. Adenitis colli
12	TW	5148/43	42	3	> 12	> 12	—, 70. 400.	
13	NH	5396/43	12	2	1	> 4	250. 110. 110. 200. 280.	Adenitis colli
14	JL	5844/43	12	2	1	10	3200. 3200. 3200. 2800. 2500. 2200. 1800. 800. 1250.	
15	AJ	6135/43	14	1	> 10	> 10	—, 1100. —, 400. 320. 360. 500. 900. 2000.	Adenitis colli
16	AN	6188/43	16	2	< 1	> 8	360. 640. 450. —, 200. 220. 360. 400.	Admitted 2 weeks after onset of scarlatina.
17	KJ	6384/43	8	3	7	> 20	360. 400. 2500. —, 1800. —, 1600. 900. 1000. 500. —, 400. —, 400. —, 500.	Otitis med. supp. Adenitis colli.
18	OJ	6525/43	7	2	2	2	560. 700. 640. —, 900. 800. —, 640. 250.	Adenitis colli
19	IR	6630/43	24	2	÷	> 6	—, —, 360. —, 500. 320.	Adenitis colli
20	JJ	6680/43	27	2	2	> 8	220. 320. 250. 250. 320. 250. 160.	
21	LC	7211/43	6	3	2	2		

22	EB	7367/43	6	2	4	> 5	450. 700. 1000. —. 900.	Adenitis colli
23	EC	7708/43	7	2	1	> 24	320. 1800. (6 weeks). 1800. —. 1800. (6 weeks). 1400. 1000.	Otitis med. supp.
24	LF	7790/43	6	2	2	8	320. 1800. 1400. —. 1800. 900. —. 640.	Otitis med. supp. Otitis. oss.
25	MH	7828/43	4	1	1	2	90. —. —. 56. —. 100. 110.	temp. (+ strept. hemolyt.)
26	BK	7896/43	4	2	÷	> 8	—. 500. —. 1800. 1000. 1800. —. 1000.	Adenitis colli
27	KJ	8090/43	15	3	2	> 3	—. 2500. 1800. 900.	
28	JJ	304/44	3	3	6	> 24	5000. 5000. —. 3200. —. —. 2000. 1600. —. —. 560. (1 mth.). 900. —. —. 800.	
29	BP	916/44	5	2	2	2	—. 900. —. 900.	
30	GN	957/44	16	2	6	10	180. 500. (1 mth.). 1800. —. 2500. —. 2800. 2800. —. 1800. 1800. 900. 500. 1800. 900. —. 280.	Adenitis colli
31	HG	1321/44	22	1	2	> 8	28. —. —. 100. —. 110. —. —. 180.	Adenitis colli.
32	IP	1388/44	22	2	< 1	8	400. 400. —. —. 360. 320.	6 days before admission fever and sore throat. 3 days before admission exanthema. Immediately after admission uremia. Fauces: + strept. hemolyt.
33	GB	6185/41 (44)	4	3	÷	4	320. 510. 510.	
34	TA	S.H. 726/43	8	2	> 28	68	(5½ mth.). 400. 505. 305. 250. 400. 320. —. 360. —. —. 290. —. —. 455. —. —. 400. —. —. 360. (2 mth.). 140. (1 mth.). 160. (4 mth.). 140.	Admitted from B.H. 3 mth. after onset of scarlatina.
35	LS	S.H. 1593/43	10	2	> 36	56	(3 mth.). 800. 640. 800. 1000. 730. —. 720. 800. 780. 640. 720. 640. 640. 1000. —. 100. 700. 400. 700. 400. 640. 450. 500. 560. 640. 560. 450. —. 560. —. 320. —. 500. (1 mth.). 250. —. 250. (1 mth.). 120.	Admitted from B.H. 3 mth. after onset of scarlatina. Tonsilectomia after 3½ mth's stay in S.H.



Table 2.  
Other cases of acute nephritis.

Nr.	Name	Case Nr.	Age	T.	Prot.	Hemat.	Infection	AST	Remarks
36	EH	S.H. 773/43	25	2	10	>52	Coryza	—, —, 320. (2 mth.). 250. 250. 320. 180. 285. 320. 180. —, 360. —, 250. (1½ mth.). 220. (2 mth.). 125 (1 mth.). 125 (1½ mth.). 250.	Strept. hemolyt. in secretion from ears.
37	IH	S.H. 940/43	5	3	1	>5	Otit. med.	130. 180. 180.	
38	EH	S.H. 1168/43	29	3	1	>12	Tons.	320. 400. 320. 400. 255. 200. 180. 320. 320. 200. 180. 180.	
39	CP	S.H. 1839/43	7	2	>2	>2	Otit. med.	900. 800.	Infection after extraction of tooth.
40	AJ	S.H. 1981/41	18	2	÷	2	Tons.	200. 200 200. 28.	
41	GP	S.H. 2006/43	7	3	8	9	Mandibular infection	1000. 560. 200. 400. 500. 450. 450.	
42	SM	S.H. 2075/43	29	2	5	>28	Tons.?	510. 320. 320. 720. 320. 255. 360. 250. 160. 160. 140. 180. 160. 220. 220 110. 160. 200. 110. 125. 200. 220. 160. 125. 90. (1 mth.) 250.	Tonsilectomia 5 mth's after admission.
43	AS	S.H. 2156/43	17	2	1	>9	Tons.	280. 280. 400. 500. 250. 200. 320. 320. 360. 500. (1 mth.). 180. —, 250.	
44	GC	S.H. 2244/43	12	3	12	>40	Tons.	200. 180. 400. 200. 360. 320. 510. 360. 320. 320. 290. 200. 320. 200. 320.	
45	IS	S.H. 62/44	8	4	4	12	Tons.	400. 360. 230. 400. 320. 100. 160. 200. 220. 220. 180. 220. 360. 250. 250. 200. 280. —, 280. 200. 160. 280. 180. 125. 180. 1000. 1600. 3600. 1200. 1450. 800. 600. 450. 650. 630. 400. 370. 500. 630. 700. 400. 500. 280. 300.	

Case No.	Sex	Age	Weight	Height	Temperature	Pulse	Respiration	Notes
47	AJ	S.H. 204/44	30	3	2	>12	Tons.	Admitted for hematemesis. One week before adm. tonsillitis, two weeks after nephritis.
48	HP	S.H. 469/44	49	3	2	6	Tons.	Admitted 3 weeks after onset of nephritis
49	EM	S.H. 459/44	10	3	>	8	Otitis med.	Admitted 9 weeks before for tussis convulsiva. No tonsillitis mentioned. Fauces normal, but hemolytic streptococci found.
50	AJ	S.H. 511/44	30	3	8	>12	Tons.	Admitted 9 weeks before for tussis convulsiva. No tonsillitis mentioned. Fauces normal, but hemolytic streptococci found.
51	GR	S.H. 592/44	46	2	>14	>14	Tons.	Admitted 9 weeks before for tussis convulsiva. No tonsillitis mentioned. Fauces normal, but hemolytic streptococci found.
52	AJ	S.H. 1981/43	18	2	>	2	Tons.	Admitted 9 weeks before for tussis convulsiva. No tonsillitis mentioned. Fauces normal, but hemolytic streptococci found.
53	AM	B.H. 2648/43	3	?	1	17	?	Admitted 9 weeks before for tussis convulsiva. No tonsillitis mentioned. Fauces normal, but hemolytic streptococci found.
54	VK	B.H. 3333/44	16	16	2	8	Tons.	Admitted 9 weeks before for tussis convulsiva. No tonsillitis mentioned. Fauces normal, but hemolytic streptococci found.
55	KA	B.H. 6592/43	7	3	>	4	Tons.	Admitted 9 weeks before for tussis convulsiva. No tonsillitis mentioned. Fauces normal, but hemolytic streptococci found.
56	EA	B.H. 6971/43	12	3	2	>3	Tons. ?	Admitted 9 weeks before for tussis convulsiva. No tonsillitis mentioned. Fauces normal, but hemolytic streptococci found.
57	AK	B.H. 7700/43	33	2	>	2	Tons.	Admitted 9 weeks before for tussis convulsiva. No tonsillitis mentioned. Fauces normal, but hemolytic streptococci found.
58	TL	B.H. 1266/41 (43)	4	1	>	7	Tons.	Admitted 9 weeks before for tussis convulsiva. No tonsillitis mentioned. Fauces normal, but hemolytic streptococci found.
59	JJ	II 1172/43	38	3	>17	>17	Tons.	Admitted 9 weeks before for tussis convulsiva. No tonsillitis mentioned. Fauces normal, but hemolytic streptococci found.
60	VS	II 1259/43	14	4	2	>10	?	Admitted 9 weeks before for tussis convulsiva. No tonsillitis mentioned. Fauces normal, but hemolytic streptococci found.
61	PH	II 1552/43	16	4	2	>16	Tons.	Admitted 9 weeks before for tussis convulsiva. No tonsillitis mentioned. Fauces normal, but hemolytic streptococci found.

(Continued).

Table 2. (Continued).

Nr.	Name	Case Nr.	Age	T.	Prot.	Hemat.	Infection	AST	Remarks
62	KJ	II 1805/43	13	2	2	3	Tons.	200. —, 220. 250. 320. —, 220. —, 220. —, 200.	
63	IP	II 166/44	14	3	÷	8	Tons.	500. 160. —, —, 250. —, —, 180. —, —, 200.	
64	NJ	III 694/43	35	2	÷	3	Tons.	200. 160. 180. 90. 145. 130. 145.	
65	VM	III 1148/43	21	3	>16	>16	Absc. peri-tons.	145. 200. 320. 255. 320. 360. 320. 255. 290. 360. 255. 290. —, 250.	Streptoc. hemolyt. found in fauces 11 out of 12 consecutive days.
66	SH	III 1149/43	35	3	4	15	Tons.	160. 180. 160. 160. 145. 160. 130. 200. 180. 160. 160. 160.	
67	KN	III 1747/43	54	2	2	2	Tons.	320. —, —, —, 450.	
68	BR	III 1826/43	12	2	2	2	Tons. ?	—, —, 125. —, 100. 100. 140. 100.	
69	WB	VII 329/43	11	1	3	7	Tons. ?	—, —, 570. 360. 360. 360. —, 510.	
70	ON	VII 421/43	8	2	8	8	Tons.	400. 400. 320. 510. 160. 320. 200. 255. 250. 180. 230. 200.	
71	OJ	VII 607/43	13	2	>24	23	Febrile disease	—, —, 1600. —, 720. 720. 640. 570. 640. 510. 360. 455. 320. 400. 510. 360. 290. 290. 220. 280. 200. 180. 200. 200.	Admitted one week after onset of nephritis
72	AC	VII 343/44	28	?	3	>4	?	90. 130. 110. 160.	Admitted with acute itching skin affection and many inflamed ulcers. Besides a chancre (+ spir. pall.)
73	EH	B. 56/3 43	11	3	7	7	Tons.	1600. —, —, 1280. —, —, 400.	
74	RM	B. 136/5 43	15	1	1	>	5 Tons.	—, 510. 320. 455. 505.	
75	ES	B. 207/5 43	23	4	1	4	Tons.	145. —, 360. 400. 455. 400.	
76	RM	B. 146/2 44	10	4	÷	>12	Tons.	—, —, —, 200. 250. 250.	
77	RL	C. 120/12 43	20	2	10	10	Tons.	450. 900. 400. —, 500. —, 360. 360.	
78	RP	C. 148/12 43	34	4	11	11	Tons.	—, 450. 140. (1 mth.) 450. —, 250. 450. 500.	

Table 3.  
Chronic Nephritis.

Nr.	Name	Case Nr.	Age	AST	Remarks
79	AR	S.H. 2281/43	60	80. 160. 180.	Relapse Relapse
80	IO	S.H. 594/43	16	70. 70. 160.	
81	EH	S.H. 682/43	18	65. 140. 230. 200. 140. —. —. —, 180. 125. 145. 110. 90.	
82	DD	S.H. 990/43	28	200. 140. 100. 100. 80. 90. 50. 70. 130. 130. 145. 200.	Relapse
83	BJ	S.H. 1103/43	14	100. 130. 130.	
84	AA	S.H. 1167/43	66	45. 40. 35. 20. 40.	
85	CP	S.H. 1214/43	67	80. 115. 90. 80. 115. 145. 130.	
86	IP	S.H. 1351/43	55	45. 25.	
87	CR	S.H. 1391/43	59	65.	
88	RM	S.H. 1618/43	48	56. 100. 56. 56. 110.	
89	MW	S.H. 1647/43	41	180. 180. 200.	
90	RL	S.H. 1651/43	37	80. 110. 140. 90. 64. 125. 80. 125. 110. 125.	
91	FK	S.H. 1717/43	51	280. 65.	
92	ER	S.H. 1866/43	38	20. 28. 32. 36. 25. 25. 28. 25. 36. 28. 56. 56. 64. 56. 64. 80.	
93	HB	S.H. 1902/43	34	50. 64. 28.	
94	AO	S.H. 2118/43	46	0.	
95	JJ	S.H. 2226/43	71	160.	
96	AN	S.H. 2242/43	55	90.	
97	AR	S.H. 2281/43	60	80. 160. 180.	
98	LA	S.H. 164/44	76	22. 22. 45.	
99	JA	S.H. 146/44	70	28. 22. 64.	
100	SJ	S.H. 170/44	35	90. 90.	
101	SN	II 1020/43	40	80.	Relapse
102	KD	II 1654/43	72	28.	
103	LS	III 677/43	42	50. 100.	
104	HL	III 752/43	62	30.	
105	MN	VII 332/43	56	160. 100. 130. 130. 130. 100.	
106	SA	B. 10/2 44	11	64.	

No. 25 has just been referred to. Despite the finding of hemolytic streptococci in the fauces and the said complications the AST remained low.

No. 31 was a severe case of scarlatinal nephritis with uremia. Swabbing of the throat showed + hemolytic streptococci, but the AST only increased gradually from 28 to 180. This is possibly a very slow rise, later on reaching over 200.

No. 37 was observed for quite a short period only.

No. 53 is a peculiar case, whose etiology is obscure. There were hemolytic streptococci in the fauces, but during 9 weeks' stay in hospital for tussis convulsiva no signs of acute infection of another nature were noticed. The AST remained normal.

No. 68 showed a maximum value of 140. Anamnesis and course were quite typical. No examination for streptococci in the fauces was made.

No. 72. This was probably a case of acute syphilitic nephritis.

Lastly, another case is of interest in this connection (No. 66). In this case the AST only just reached 200, despite the fact that numerous throat swabs showed the presence of hemolytic streptococci.

The course of the AST-curve has also been highly varying. In a number of cases the maximum values were only reached after the course of some time. The curve is frequently notched. In case of a fairly considerable initial increase it seems to last several months generally before normal values are reached, indeed the cases observed for the longest period display persistence of increased AST for up to one year. It is impossible to ascertain any unquestionable connection between the absolute height or course of the AST-curve and the clinical course as manifested by the duration of proteinuria and hematuria. During the experimental period (about 1 year) I have myself — for the sake of uniformity — performed a weekly microscopy of all urines of patients with renal disorders in the medical ward of the Sundby Hospital. These examinations showed that there was also no connection between the AST-curve and the degree of hematuria, no more than between this curve and the duration or the degree of pyuria and cylindruria.

In 4 cases tonsillectomy was made in the course of the nephritis. In 2 of these cases (No. 35 and 44), in which the AST-determinations are sufficiently frequent to allow of judgement, a decrease of the AST seems to occur after that interference.

Almost all the cases of chronic nephritis showed values below 200. One out of 28 cases showed a value of 280 on one occasion, 2 had only just 200. — S.H. 990/43 was a woman, aged 28, who throughout several years had displayed signs of increasing renal insufficiency. No fresh infection. The pt. died in the ward of uremia.

— S.H. 1647/43 was a man, aged 41, who in 1938 had been admitted with chronic latent nephritis. He is admitted now after a fainting fit. No signs of fresh infection. — S.H. 1717/43 was a woman, aged 51, whose renal disorder was diagnosed in 1938. Admitted with increasing cardiac insufficiency. No signs of acute infection.

4 cases were perceived as relapse in a chronic nephritis. 3 of the cases were young people who some years ago had had nephritis and who again, after an interval without any subjective inconvenience, developed signs of nephritis. VII 332/43 was a middle-aged man, whose nephritis was ascertained 8 years previously and who now got a recrudescence of his symptoms after an acute enteritis. In one of these pts. an increase of the AST was found (S.H. 682/43); he was a man, aged 18, who had had nephritis at the age of 4 years. The urine had not been examined since. He got a slight cold 2 days before admission. There was proteinuria of short duration, constant slight hematuria, normal blood-pressure, and urea clearance.

### Discussion.

As regards the etiological question the result of the present examination decidedly indicates that in by far most cases of acute nephritis we have to do with a sequela of an acute infection with hemolytic streptococci. Only 6 out of the 78 cases of acute nephritis had no increase of the AST. 3 of these 6 cases had hemolytic streptococci in the fauces and may, therefore, probably be considered »poor anti-body formers». 1 of the remaining 3 cases possibly had a syphilitic nephritis. Cases of non-streptococcal nephritis thus occurred in this material in 5 to 10 per cent. of the cases at the utmost.

It is, of course, a question whether that which is determined has anything at all to do with the renal disorder, whether it is not simply the AST-increase after an acute streptococcus infection. If the present material is compared with Winblad's (1941) and Kalbak's (1942) tonsillitis and scarlatina material we do not get any convincing impression, at any rate as far as scarlatina is concerned, of the AST-curve being very different when the disease is complicated with nephritis and when it is not. As far as tonsillitis is concerned such comparison is difficult, as for unknown reasons

Winblad seems to find far higher values in that disorder than Kalbak does.

Moreover the material proves the justification of ascribing no slight importance to AST-determinations when the question of acute or chronic nephritis has to be settled. Only 4 out of the 28 cases of chronic nephritis displayed an increased AST, and the 2 of them only just 200. When this is compared with the result of the examination in acute nephritis it must be concluded that in this differential diagnosis the occurrence of an increased AST points to the presence of an acute disease, while a normal AST suggests a chronic condition. The AST-determination thus becomes of importance when the question, so important individually and socially, has to be decided, whether the pt. has to stay in bed for months or his disorder may be considered refractory to his staying in bed or to ordinary hospital treatment. In making this decision we must, however, of course consider the possibility of streptococcal infections previously passed off, and of no consequence in this connection, as well as the fact that in a small percentage of apparently normal individuals an increased AST is found.

### Summary.

In a number of patients with acute and chronic glomerular nephritis weekly AST-determinations were made. 6 out of 78 cases of acute nephritis had a normal AST. 3 of them had hemolytic streptococci in the fauces, 1 pt. probably had an acute syphilitic nephritis. 4 out of 28 cases of chronic nephritis had a slightly increased AST.

It is concluded that acute nephritis is almost always a sequela of an infection with hemolytic streptococci and that AST-determinations are valuable in the differential diagnosis between acute and chronic nephritis.

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(The Factory Inspection Board of Oslo.)

## Welding regarded from the Medical Point of View.

By

EILER H. SCHIÖTZ.

(Oslo Arbeidsnemnd.)

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Although the operation of welding is not reckoned among the most dangerous trades, yet it may give rise to several forms of poisoning, or occupational diseases. The knowledge of these disorders is not very widespread among medical practitioners, and the purpose of the present article is to give a survey of these questions, together with an account of the author's own observations.

### Autogenous welding.

*Gas-welding or autogenous welding* is effected by means of a blow-pipe to which is conveyed an inflammable gas (in most cases acetylene) and oxygen in suitable proportions — usually in equal parts. The flame has a very high temperature: 3500—4000°C. After the part that is to be welded has been heated up to melting-point, a suitable quantity is melted off from a welding rod, so as to become fused with the pieces of metal under treatment, and the two parts are thus made to unite. Autogenous *cutting* is employed especially for dividing and shaping pieces of steel and gives a very even and smooth cut-surface. The material is first heated up by means of a blow-pipe until it becomes incandescent, and a thin jet of oxygen is then directed against the glowing metal.

Poisoning or occupational diseases among welders using the autogenous method may be due to: 1. Acetylene or possibly existing impurities therein. 2. Gases evolved in the welding flame. 3. Fumes and gases from the piece of metal under treatment.



### 1. Acetylene and possible impurities therein.

Acetylene,  $C_2H_2$ , is an unsaturated carbohydrogen compound having narcotic action (cf. the use of Narcylen in surgery). The narcotic effect is due to the air being deprived of oxygen. A concentration of 33 per cent leads (according to Davidson) to loss of consciousness within 7 minutes. A mixture of acetylene and oxygen is explosive if the acetylene concentration is greater than 2.5—3 per cent. Thus in the presence of open fire explosion will take place long before the concentration becomes otherwise dangerous. So far as can be seen, only one case of poisoning which must presumably be ascribed to acetylene is reported to have occurred among welders (Wirtschafter and Schwartz). In that case the welder had shut off the cock for supply of oxygen, while the cock for acetylene remained open.

The possible presence of *impurities* in the acetylene is a matter of greater interest from a medical stand-point. In unrefined acetylene there may be present such highly poisonous gases as phosphoretted hydrogen ( $PH_3$ ), arsenuretted hydrogen ( $AsH_3$ ), sulphuretted hydrogen ( $H_2S$ ) etc. in quantities which vary greatly according to the quality of the carbide from which the acetylene is obtained. The Elektrochemische Gesellschaft in Hirschfelde (Saxony) has stated that the  $PH_3$  concentration amounts to from 0.02 to 1.8 per cent and that the  $H_2S$  concentration lies between 0.01 and 1.3 per cent. In the literature there are reported several cases of poisoning during welding which are ascribed to these gases, but the causal connection often seems doubtful. Most of the cases are certainly due to other gases (cf. section 2). In the appended list of publications reference is made to the authors whose published cases must presumably or possibly be attributed to impurities in the acetylene. Nowadays there is almost always used *purified* acetylene compressed into steel containers, the so-called »dissous gas», which contains quite insignificant and absolutely harmless concentrations of the above-mentioned gases (for example, in Norwegian »dissous gas» 0.0017 vol. per cent of  $PH_3$ , 0.0008 vol. per cent of  $H_2S$  and non-demonstrable quantities of  $AsH_3$ ).

### 2. Gases evolved in the welding flame.

*a. Carbon monoxide* has formerly been regarded as one of the principal causes of poisoning during welding, especially in confined spaces.

*Complete* combustion of acetylene proceeds according to the following formula:  $2 \text{C}_2\text{H}_2 + 5 \text{O}_2 = 4 \text{CO}_2 + 2 \text{H}_2\text{O}$ . In the inner zone of the welding flame an *incomplete* combustion takes place, as equal parts of acetylene and oxygen are employed. The combustion formula here is:  $\text{C}_2\text{H}_2 + \text{O}_2 = 2 \text{CO} + \text{H}_2$ . Meanwhile the combustion of CO continues to take place in the outer zone of the flame by aid of the oxygen in the air.

Even when the welding takes place in small, unventilated rooms and although, as appears from the above formula, the welding flame deprives the air of  $1\frac{1}{2}$  times as much oxygen as is conveyed to the burner from the oxygen-container, practical experiments (especially those made by Rimarski & Konschak) have shown that there never occur CO-concentrations exceeding 0.01 per cent, which is the upper limit usually fixed by occupational hygienists for the concentration if the work is to be continued for several hours without deleterious results. It was only when the flame was allowed to burn freely for over five hours in an airtight room (which, of course, never occurs in practice) that the CO-concentration rose to above 0.01 per cent, but that experiment also showed that before the concentration of CO reached dangerous degrees the air became insupportable owing to accumulation of carbon dioxide. — In the literature there have earlier been reported numerous cases of poisoning which are ascribed to CO, but which accordingly must have had other causes.

b. *Nitrous fumes* (oxides of nitrogen) constitute the chief danger in autogenous welding or cutting in confined spaces, a risk to which the English Chief Inspector of Factories, J. C. Bridge, was the first to draw attention in 1934. (The well known toxicologist Zangger in Zürich had been in touch with this idea a year earlier.)

It has long been known that nitrogen and oxygen at high temperatures can form *nitrogen monoxide*;  $\text{N}_2 + \text{O}_2 = 2 \text{NO}$ , an endothermal reaction. But this gas is very unstable and easily breaks down to nitrogen and oxygen again. Large quantities of NO are evolved only when the gas is rapidly removed from the zone of reaction and cooled off. In autogenous welding the possibilities for formation of NO are certainly present: The temperature is very high; nitrogen occurs in small concentrations as impurities in the oxygen (in Norwegian oxygen 0.33—0.41 per cent) and in the acetylene, and may also possibly be derived from the air; owing to the eddies of air around the flame the gas is at once reduced to a low temperature. — This primarily formed gas (NO) rapidly becomes oxidized by the oxygen in the air to form nitrogen peroxide ( $\text{NO}_2$  or  $\text{N}_2\text{O}_4$ ), a brownish gas with pungent odour.

Only extremely small quantities of  $\text{NO}_2$  are required to produce symptoms of poisoning. According to Henderson & Haggard irritation of the throat may be produced by 0.006 vol. per cent and coughing by 0.01 vol. per cent. A concentration of 0.012—0.015 vol. per cent is dangerous even when the action of the gas lasts only a short time, and with concentrations of from 0.012 to 0.015 vol. per cent a fatal effect is rapidly produced. The maximum concentration that can be continuously inhaled without injurious results has been estimated by the Massachusetts Division of Occupational Hygiene to be 0.001 vol. per cent (Case & Castrop).

Quantitative determinations of nitrous gases evolved during the operation of welding have been carried out on a minor scale by Bridge, by Maenicke and by Kienitz and on a larger scale by Rimarski & Konschak. The conclusion drawn from these investigations is that in autogenous welding and cutting of metals nitrous gases are *always* produced, and further that the quantity evolved increases according to: 1) the duration of the work, 2) the size of the burner employed, 3) the time in which the flame burns freely, 4) the decreasing purity of the oxygen. Practical experiments have shown that in spite of the use of a ventilator, or even of compressed air, during welding operations in a boiler there may arise alarming or dangerous concentrations of nitrous gases. With use of very large burners a fatal concentration may be produced after only fifteen minutes' work in a confined space (for instance, in the hold of a ship), unless care is taken to provide for effective ventilation. In case of cutting or burning of metals the concentration is slightly less than in welding.

On going through the cases of poisoning during autogenous welding or cutting that have been published since these working processes came into general use in the years from 1915 to 1920 it will be seen that many of the poisonings which from time to time have been ascribed to a great variety of causes (acetylene, acetylene impurities, carbonic oxide, acroleine, »Reizgas») may safely be assumed to have been caused by nitrous gases. In a monograph published by the present writer in 1940 (in »Nordisk Hygienisk Tidsskrift») there is given a tabular survey of 22 different publications, comprising altogether 53 cases of poisoning during the process of autogenous welding where nitrous gases constitute by far the most probable cause, and since that time a number of additional

cases have been reported. In this respect the reader is referred to the appended list of publications.

An account of the symptomatology and the pathological anatomy in cases of poisoning by nitrous gases will be found in a previous article in this journal by Torsten Lindqvist.

### 3. *Fumes and gases from the piece of metal under treatment.*

In the welding or cutting of *clean metals* vapours do not arise, as the metal is heated up only to melting point, and the vapour tension is therefore practically equal to 0. But poisonous vapour may arise from the *coatings of metals*. In autogenous welding or cutting of metal painted with red-lead ( $\text{Pb}_3\text{O}_4$ ) or white-lead ( $2\text{PbCO}_3 + \text{Pb}(\text{OH})_2$ ) very large quantities of lead oxide vapour are given off and thus there arises a great risk of *lead poisoning*, as oxide of lead begins to give off vapour at a temperature of from  $750^\circ$  to  $800^\circ$  C. and boils at about  $1470^\circ$  C., while iron does not melt before reaching about  $1500^\circ$  C. E. W. Brown in 1926 describes how 49 per cent of 221 men engaged in autogenous welding at an American shipyard were attacked by lead-poisoning in the course of 8 months, causing a loss of altogether 2,105 days of work. In the annual reports for the years 1923—1940 from the Chief Inspectors of Factories in Norway 33 cases of lead poisoning or other disorders caused by lead after that kind of work are recorded, but this figure certainly represents only a minor part of the actual number of cases.

Coatings on metals may also give rise to *metal fume fever*, especially in the form of *zinc fever* («founders' ague»). This disease may also arise in the welding or cutting of galvanized (*i.e.*, zinc-plated) sheets of iron, or when the metal is coated with zinc-white, likewise when working with *alloys* containing zinc, such as brass (copper and zinc) or nickel silver (copper, zinc and nickel). To obtain the melting-point of brass it is necessary to heat the alloy up to a temperature of about  $850^\circ$  C., that is to say, almost up to the boiling-point for zinc ( $930^\circ$  C.).

*Acrolein poisoning* is said to occur in the treatment of heated metals coated with oil or grease. The toxic concentrations of acrolein (acrylaldehyde,  $\text{CH}_2=\text{CH}\text{CHO}$ ) are supposed to be like those of phosgene (during the previous World War this gas was used by the French in gas attacks),

and it has a highly irritant action on the mucous membranes (eyes and respiratory tract).

*Carbon monoxide poisoning* may arise in case of incomplete combustion during the welding or cutting of metals coated with carbonaceous substances (Schwarz).

*Cases of poisoning by nitrous fumes during autogenous welding or cutting of metals in Norway.*

On going through the annual reports from the Chief Inspectors of Factories for the past 20 years there were found records of several cases of poisoning during autogenous welding or burning which are of immediate interest. Regarding some of these cases supplementary particulars were obtained from hospitals or in the records of the State Insurance Office.

*Cases 1 and 2.* (Claims No. 5560 and 5558, 1924, State Insurance Office.) One forenoon in August 1924 a man aged 42 was engaged, together with another, in burning out rivets in the boiler of a donkey-engine on a boat in Fredrikstad. During this work compressed air was conveyed to the boiler. The work lasted about 1 ½ hours, during which time they are said to have noted no symptoms of illness. After having come out, they felt a little «queer», but were well enough to be able to wash themselves, draw their week's wages and walk home (about 2 ½ km). A couple of hours after finishing the work the first-mentioned man began to breathe very heavily. He got a cough with yellowish-red expectoration, the symptoms gradually became more severe and he died of pulmonary edema in the presence of the doctor — in spite of treatment with camphor injections and other stimulants — about seven hours after conclusion of the work. The doctor who treated him expressly states in his report that there was no sign of carbon monoxide poisoning (as had been suggested by the inspector of explosive and inflammable materials), but that «irrespirable gases... had had an irritating action on the bronchi... so that there arose symptoms of inhalation pneumonia which... was accompanied by acute pulmonary edema».

The other man became short of breath on his way home, felt sore in the throat and got a dry hacking cough, increasing in intensity during the afternoon and evening. The doctor who was called in, found him half sitting up in the bed, and he was then so short of breath that he could only speak a couple of words at a time. The respiration was superficial (40), the pulse good (84). No abnormal sounds over the lungs. On the following day numerous bronchitic sounds were to be heard over the posterior surface of both lungs, as well as moist râles and frictional sounds over the right lung. The pulse was then 100, the temperature normal. In the course of the following days the symptoms gradually subsided, and he was able to get up on the 9th day after the poisoning. For some time afterwards he felt languid and got short of breath when walking, but was fit to resume

his work on the 23rd day after the mishap. The doctor who attended him, gives no diagnosis in his report to the State Insurance Office, but merely remarks that it was «a case of poisoning for which no explanation has hitherto been found».

Cases 3 and 4. (Annual Report from the Chief Inspector of Factories, 1930, p. 58.)

«Two workmen were engaged in burning with autogenic flame through manganese steel castings with an underlayer of zinc. After having worked for about 4 hours one of them felt ill, having a *dry cough*<sup>1</sup> and presumably headache and feverishness. On resuming the work he again felt ill, so that he had to go home. The other man became *violently sick on the day after the work of welding was finished*,<sup>1</sup> with headache, nausea, vomiting and fever. *Both of them complained of dyspnea*.<sup>1</sup> The illness is presumed to be due to inhalation of zinc vapours.»

It has unfortunately not been possible to obtain further information regarding the circumstances under which the poisonings occurred or about the subsequent course of the illness. It is possible that some of the symptoms may have been caused by zinc oxide («zinc fever»), but this diagnosis is not fully satisfactory. The probability is that nitrous fumes have been a contributory factor.

Case 5. (Claim No. 1221/1934, State Insurance Office.) A welder in Lillehammer was on the 14th February 1934 engaged in autogenous welding of the coupling-muffs of pipes in the interior of three oil-tanks, about 2.5 metres long and about 1 metre in diameter and provided with a man-hole (size not stated). During the work the tanks had to be gradually rolled round by another workman, so that the part to be welded was constantly being turned upwards. One half-turn of the tank brought the manhole to lie underneath, so that the interior of the tank was almost entirely cut off from air supply. The man could not keep on working for more than 15 minutes at a time without getting fresh air. The work inside in the tanks took altogether about an hour and a half. He started to work at 8 a.m. and after the lapse of a couple of hours he began to find it difficult to breathe. At 1 o'clock he was allowed to go home from the workshop on account of a constant irritating cough and difficulty in breathing. A doctor was called in the same evening, and two days later the man was sent to hospital. On admission he had distinct dyspnea and was slightly cyanotic. Pulse 104, temperature 37.3° C. Numerous râles were heard over both the anterior and the posterior surface of the lungs. During the first days in the hospital he had considerable dyspnea and coughed up large quantities of frothy, red-coloured sputum. After treatment with stimulants (coramin etc.) his condition rapidly improved. X-ray examination of the lungs twelve days after the accident revealed a somewhat «fluffy» shadow outside of each hilus, most marked on the right side. He was discharged from hospital on the 27th of February, 13 days after the poisoning occurred, with the diagnosis: *toxic edema of the lungs*. In a subsequent report to the Insurance Office

<sup>1</sup> Italicized by the present writer.

(dated 1st October 1934) the doctor who treated him in the hospital stated that the patient was not completely cured; he still complained of shortness of breath after exertion and had less power of endurance than before. For example, he had to give up his gymnastic exercises. In reply to inquiries he states in a letter dated January 28th 1943 that he still has the same symptoms and that since the poisoning he has been very liable to get severe attacks of coughing. (It has sometimes happened that I got such a fit of coughing that I fell down in the street, but fortunately it has very seldom been so bad as that.)

*Case 6.* A workshop foreman was one day in December 1939 engaged in welding operations in an experimental laboratory about 80 cubic metres in size. After about one hour's work he got an irritating cough and had difficulty in breathing. He went out into the fresh air for fifteen minutes and then tried to work again, but in vain. After resting a while longer he proceeded with the work for about an hour. On his return home he got severe fits of shivering and had a general feeling of illness, slept badly in the night, but had more or less recovered the next morning. Three other welders in the same room had coughed a good deal and felt unwell, but were not obliged to discontinue their work.

*Cases 7—10.* In the evening of January 18th 1940 two welders and two platers started to burn out rivets in the forepeak of a ship in one of the Oslo shipyards. After about twenty minutes they had to go up into the fresh air on account of shortness of breath, painful coughing, nausea and «running from the eyes». A fresh attempt 45 minutes later had to be abandoned owing to violent fits of coughing and a third unsuccessful attempt was made after a couple of hours. They then had to discontinue the work and went home. One of them was able to resume the work nine days later (after getting treatment at home), but then only with difficulty, the others after a couple of days.

*Cases 11—13.* On March 5th 1941 three welders, relieving each other every ten minutes, were engaged in burning off a layer of pitch and beer-scale in a tank, about 5 metres long and about 2.5 metres in diameter, provided with a manhole of about 0.3 m<sup>2</sup>, just barely large enough to allow a man to enter. The tank was supplied during the work with fresh air from a compressor. A large welding blow-pipe was employed. After from about 1 ½ to 2 hours the men began to feel symptoms of poisoning.

B. H. was inside the tank for 45 minutes altogether and appears to have held the air-tube before his mouth the whole time. He got ill during the work, became «green in the face», coughed and vomited. He remained, however, at the place of work for altogether 6 ½ hours, and walked from there to a doctor. He was advised to go to hospital, but declined to do so. He was then given an injection of morphia (1) and afterwards walked home. In the course of the afternoon he became very ill and coughed up a frothy sputum. His breathing got more and more laboured and he died before the ambulance came to take him to hospital. *Post mortem examination* made (by Dr. E. Hoel) the next day revealed, among other things: Unusually extensive death-stains. Closely situated small hemorrhages at

several places on the skin, especially over the shoulders, as well as on the conjunctiva. Very pronounced edema of the lungs. Edema and fairly great hyperemia in the cerebral membranes. No macroscopically visible hemorrhages in the brain. The blood had «a peculiar cherry-red colour». Conclusion: The immediate cause of death is an exceptionally severe pulmonary edema, due to inhalation of nitrous fumes and phosgene. (Klaus Hansen, professor of pharmacology, states in his report that «experience shows that acetylene gas not infrequently contains phosgene», which is not correct.)

The second welder A. L., asked the same evening to be sent to hospital (Ullevaal, Dept. VIII), chiefly because of his workmate's death. He had been in the tank for about 2 ½ to 3 hours in all. In the end he got sensations of great constriction over the chest, as well as bleeding from the nose (a thing he had never had before), had a dry cough and was unable to eat. In the hospital there was found: greatly injected uvula, insignificant crepitation on the posterior surface of the right lung, temp. 37.9° C., S.R. 14 mm., otherwise no abnormal findings. At his own wish he was discharged the next day, being then perfectly well.

The third welder O. M. was working for altogether 70—80 minutes inside the tank and had the same symptoms as the preceding patient. He too desired to be sent to hospital (Aker Hospital) on account of the death of his workfellow. In the middle of the night he got an attack of coughing accompanied by uneasiness, slight sensations of constriction over the chest and a little headache, and he was given 1 cm<sup>3</sup> of morphia. Next forenoon he had a few slight attacks of dry coughing. Nothing pathological was found on clinical examination, and after 5 days he was discharged from hospital and at once began to work again. In the first time after beginning his work he easily got tired and now and then he felt a stinging pain in the left axilla.

### Electric welding.

*Electric welding* or *arc welding* is performed by means of an electric arc as source of heat. This arc is usually produced between an electrode and the piece of metal to be welded and has a temperature of from 3000° to 4000° C. The electrode now used most often consists of material similar to the metal under treatment. It may be *uncovered* or be *covered* by a coating of greatly varying composition.

Poisoning, or occupational diseases, among electrowelders may be due to: 1. Inhalation of «welding fume». 2. Rays from the arc flame.

#### 1. Inhalation of «welding fume».

«Welding fume» is a dense, white, grayish-white to yellowish or brownish vapour of extremely variable composition. It contains



gases evolved in the electric arc, vapours from the electrode metal or the coating thereof and from the piece of metal that is being welded.

a. *Gases from the arc flame.* That *nitrous fumes* arise in the electric arc has been known for over 100 years. The first who drew attention to the fact that this is also the case in arc welding was the Austrian engineer Franz Osswald (1928). This has since been confirmed by many investigators (including Titus, Warren & Drinker, MacQuiddy and collaborators, Weber & Yende, Case & Castrop, Rimarski & Konschak). If animals are experimentally exposed to inhalation of welding fumes (filtered or unfiltered) they often die of bronchopneumonia and pulmonary edema owing to the nitrous gases contained in the fumes. Investigations of gas concentrations in the workshops have shown, however, that there is very seldom any risk of poisoning by nitrous gases during arc welding. Cases which may possibly be attributed to this cause have been reported by Adler-Herzmark, Williman, in »Der gewerbeärztliche Dienst» and by Jacobsen. The pathological pictures in these cases can, however, be interpreted in various ways and the etiology is uncertain.

b. *Fumes from the electrode metal or the coating thereof.*

The *uncovered electrodes* are made of steel of somewhat varying composition. The metal may contain small quantities of manganese (0.3—0.6 per cent, in certain special electrodes over 1 per cent), phosphorus, sulphur, carbon, silicon, copper, nickel, chromium or cadmium.

The *coating on the electrode* is of highly variable composition, which is kept secret by the makers. Silicic dioxide is practically always one of the constituents (15 to 38 per cent  $\text{SiO}_2$ ). Manganese and iron are also often added, less frequently titanium and fluor (the coating of certain special electrodes used for welding aluminium and rustproof steel, however, contains considerable quantities of fluorides). Those who are specially interested in this matter may consult the publications of Weber & Yende and of Case & Castrop.

It will be seen from the foregoing that the fumes from the electrode vary too much in composition to admit of giving generally applicable figures of analysis. The main constituents are: *ferric oxide* (50—97 per cent), *silicic dioxide* (0.5—21 per cent), *manganic oxide* (1—26 per cent), and *calcic oxide* (0—26 per cent). More detailed particulars are given in the authors's afore-mentioned monograph.

In no other occupation are the workers liable to inhale such large quantities of ferric oxide as during electrical welding in confined spaces, and after years of work under such circumstances there may arise *siderosis of the lungs*, an occupational disease which was first detected among electric welders in England by Doig & McLaughlin (1936). These two investigators, however, were not quite clear as to the causative relation. They discuss the possibilities of silicosis, asbestosis and siderosis. Cases of siderosis among electric welders have later been reported by Britton (1936), Hollmann (1937), Enzer & Sander (1938), Killick (1938), Sander (1939), Britton & Walsh (1940), Schiötz (1941), Koelsch (1941), Saupe (1941) and Breitenbach (1942). Subjective disorders in connection with this condition are rarely seen, but may appear if the siderosis is very pronounced (cf. Koelsch). Small quantities of iron in minute particles, visible on X-ray photographs, may be absorbed in the course of a short time (Bentzen). The iron is hardly likely to occasion fibrosis, such as is to be seen in case of silicosis. Meanwhile the possibility that the silicic dioxide from the coating on the electrode may play a contributory part cannot be entirely precluded. In exceptional cases inhalation of large quantities of ferric oxide at a time may give rise to metal fume fever (Holstein).

Whether the content of *manganic oxide* in the fumes can bring about occupational diseases is an undecided question, but it is very unlikely. Symptoms from the extrapyramidal nervous system, in the form of Wilson's disease, have not been reported to occur among electrical welders (Beintker's cases are doubtful). Continual inhalation of manganic oxide can, as is known, greatly increase the predisposition to croupous pneumonia (cf., among others, Elstad in «Nord. Med.» 1939). Hyperfrequency of pneumonia among electric welders has been reported by Westhofen, Humperdinck, Teleky and Pozzi, but these publications are not convincing from a statistical point of view.

It is a known fact that the welding fumes often have an irritating effect on the *upper air-passages* (Bridge, Westhofen, «Der gewerbeärztliche Dienst» 1935—36, Weber & Yende). Several factors probably come into play here: oxide of calcium and metallic oxides (including cadmic oxide) from the electrodes and from the metal that is being welded, and possibly also nitrous fumes in small quantities.

*Digestive disorders* are sometimes very much in evidence among electric welders (Humperdinck, Weber & Yende, Rösing). In Rösing's investigations at the Krupp Works in Essen there was found a striking difference between electric and autogenic welders as regards the frequency of digestive troubles (37 per cent and 11 per cent respectively), and the cause was here assumed to be chiefly the fumes from coated electrodes. The frequency was said to be far less when uncoated electrodes exclusively were employed.

c. *Vapours from the metal that is being welded.* The risk of lead-poisoning and zinc fever is perhaps somewhat greater than in autogenous welding, as the metal is heated up to higher temperatures.

## 2. *Rays from the arc flame.*

The intensity of the *ultra-violet* rays is over 100 times greater in arc welding than in autogenous welding (Lipkowitsch), which explains why *electric ophthalmia* far more frequently occurs during the former process. An investigation carried out by the author through inquiries addressed to 270 electric welders showed that 62 per cent of them had one or more times suffered from electric ophthalmia («welder's blindness») as an occupational disease. This accords well with the result of investigations made in Russia by Lipkowitsch (67 per cent) and by Natanson & Winigrow (70 per cent). The latter found in 25 per cent a «chronic electro-ophthalmia» with injection of the conjunctival and ciliary vessels, while several workmen had minute obscurations in the lens, detectable by means of the split-lamp. In case of more intense action of light the fundus of the eye may suffer permanent injury, but this is extremely rare. Cases have been reported by Thies, Roy and Ochi.

The *infra-red* rays in the arc flame can hardly be supposed to play any important part as regards the etiology of eye diseases in electric welding. Cases of occupational cataract such as may occur among glass-blowers and employees in smelting works have not been reported among electric welders.

As regards the *hygienic precautions* demanded during the operation of welding, the author's previously mentioned monograph may be consulted.

## Summary.

### *Welding from Medical Point of View.*

Poisoning or other occupational diseases among *autogenic welders* and *burners* may be due to:

1. Impurities in unrefined acetylene: phosphoretted, arseniuretted or sulphuretted hydrogen.
2. Gases evolved in the welding flame: nitrous fumes.
3. Vapours or gases from the metal which is being treated: metal oxides (especially oxides of lead and zinc), acrolein, carbon monoxide.

From his own observations, from the records of the State Insurance Office and from the annual reports of the Chief Inspector of Factories the author has collected 13 cases of presumable poisoning with nitrous fumes during autogenic welding and burning which occurred in Norway in the last 20 years, two of them with fatal issue. Case-histories and clinical findings are reported.

Poisoning or other occupational diseases among *electric welders* may be due to:

1. Inhalation of »welding smoke», which consists of: a. Gases from the arc flame (nitrous fumes, mostly in infinitely small quantities). b. Vapours from the electrode metal and from the coating of the electrode (oxides of iron, manganese, calcium, fluor, titanium etc.). Siderosis pulmonum has not infrequently been noted among electric welders. Irritation phenomena in the upper air-passages and digestive troubles are often prominent features. c. Vapours from the metal which is being welded (as in autogenic welding).

2. Rays from the arc flame: especially ultra-violet rays, which give rise to »electric ophthalmia», a disorder frequently occurring among electric welders (»welder's blindness»).

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From the Medical Clinic of the Serafimer Hospital, Stockholm.  
(Head: Professor A. Kristenson.)

## Exudative Pleuritis as a Symptom in Cases of malign Lymphogranulomatosis.

By

TORSTEN BRUCE.

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### Historical.

In the year 1832 Hodgkin gave a clinical account of 7 cases of peculiar lymph gland swelling. In 1865 Wilks described 13 similar cases that he designated as »Hodgkin's disease». When in 1936 Fox examined histological preparations from Hodgkin's own cases he found that only 3 of the 7 cases were to be described as what we mean by lymphogranulomatosis. The other cases comprised tuberculosis, syphilis and leucemia. During the 19th century Virchow in 1863 and Kundrat in 1893 carried out a histopathological differentiation of various types of lymph gland swelling included in Hodgkin's original description. Sternberg also distinguished a particular type of disease when in 1898 he gave a careful description of a histologically clearly delimitable tissue change of granuloma type. In 1909 Palttauf gave this the now generally accepted name of *lymphogranulomatosis*, »Sternberg-Paltaufsche Krankheit».

I do not propose here to go into the disturbances that are pathologico-anatomically characteristic of lymphogranulomatosis. The actual nature of the disease has been much discussed. What now appears to be the generally accepted view is that lymphogranulomatosis is a systemdisease in the lymphohemopoetic apparatus



that is provoked by an as yet unknown germ. The persons who contract it must have a special disposition of the lymph system if the infectious process is to develop. It is deserving of mention, however, that lymphogranulomatosis is still regarded, even by some modern researchers, practically as a malign tumour.

The typical *lymphogranulomatosis* is characterized by an *increase in the growth of the organs of the lymphatic system*, with swelling of superficial and mediastinal lymph glands and enlargement of the spleen as prominent symptoms. The lymphogranulomatosis changes often extend, however, beyond the lymph glands — so-called *extra-glandular lymphogranulomatosis*. Such changes have now been described in all the organs of the body, even if in certain cases only as an exception. The granulation process progresses from the lymphoid tissue to that of the various organs, that is pushed aside and sometimes destroyed. Extra-glandular lymphogranulomatosis appears but seldom as an independent clinical disease. The localizations that in the first place occur in cases of »primary» extra-glandular lymphogranulomatosis are stomach and intestine, lungs, skin and skeletal system.

In not a few cases *the lungs are involved in the lymphogranulomatous process*. Different writers give this as between 9 % (Gilbert) and 30 % (Sternberg); and on an average one may estimate the lungs to be involved in the lymphogranulomatosis in about 20 % of cases. The disease reaches the lungs either by direct progression from nearby mediastinal lymph glands or by way of the blood vessels.

A *primary localization of lymphogranulomatosis in the pleura* has probably not been described. The disease reaches the pleura from some organ in the vicinity of the pleura. The visceral pleura may be involved in the lymphogranulomatous process from a focus in the lung; the parietal pleura may be involved in the process through an aggressive growth of lymphogranulomatosis in mediastinal and axillary lymph glands or costal foci. Judging from information in the literature, it is much commoner for the visceral pleura to be involved in the morbid process than for the parietal pleura.

*Lymphogranulomatosis occurs in the pleura in different anatomical variants*. According to Versé 1931, the foci may constitute milary nodules, small granulated formations, or may occur in larger, knottier forms. Through the growth of the granulation tissue the pleura may become the seat of a diffuse infiltration and thickening

that, if the pleural laminæ are joined, may form connected scar-like masses.

*The clinical symptom that in the first place draws attention to the pleura is the discharge of fluid in the same.* As a matter of fact, this symptom is not uncommon in cases of lymphogranulomatosis. In 1921 Lemon & Doyle demonstrated liquid in the pleura in 4 of 26 patients, Whitacker in 1923 in 7 of 40 patients, Wright 1938 in 17 cases of 60 with intrathoracic changes and Ratkóczy 1940 in 13 of 64 clinically carefully examined cases. In such tabular presentations, however, a number of cases are undoubtedly included in which the lymphogranulomatous process has not progressed to the pleura itself, but in which the discharge of fluid is of a more transudative nature, caused by an interference in the drainage of the tissue fluid resulting from lymphogranulomatous changes in the intrathoracic lymph glands themselves or owing to the compression by the swollen glands of ductus thoracicus, venae anonymæ or vena azygos. This emerges from investigations carried out on section material by Ceelen & Rabinowitsch 1917 and Versé 1931.

The exudate that is formed in cases of pleural lymphogranulomatosis does not stand in a direct quantitative proportion to the anatomical extension of the disease in the pleura. Thus, Fraenckel & Much in 1910 found in one case only 200 ml of fluid, although a large part of the pleura was coated with lymphogranulomatous nodules. In other patients, e.g. in a case described by Düring in 1918, the reverse relation obtained. Sometimes the exudation is considerable, as in a case described by Dietrich in 1912, where quantities of fluid amounting to over 2 litres were drained off and replaced in a short time by newly formed exudate. The exudates generally have a serous character; v. Hecker & Fischer 1922 and Ratkóczy 1940 described cases in which the fluid was serously hemorrhagic.

### Author's material.

An account will be given in the following of *two cases of lymphogranulomatosis in which during one phase of the disease symptoms from the pleura were predominant.*

*Case 1. Female office-worker, born 1912.* No tuberculous heredity. No blood diseases in the family. In the summer of 1936 incipient tiredness; found difficulty in managing her work. Consulted a doctor, who palpated

*lymph glands in the neck* and performed a *test excision* on the 20/7 1936. The *histological picture* showed *lymphogranulomatosis* in an early stage. The patient received X-ray treatment, after which the lymph glands were so reduced in size that it was no longer possible to palpate them. Patient was subjectively healthy until the summer of 1937, when enlarged lymph glands appeared in the left axilla. After renewed X-ray treatment once more free of symptoms. — In October 1937 had a *feeling of stitch* in the left side of the chest. X-ray of the lungs on the 18/10 1937: left diaphragm drawn up and adhering to the thoracic wall. In the posterior sinus diffuse density. No changes in the lung parenchyma. *Pleural puncture* was performed and a *clear, light yellow exudate* drained off. At Christmas 1937 a period of fever. X-ray of the lungs on the 13/1 1938: centrally in the lung field somewhat marked streaky structure. No definite contours of lymph glands, and no signs of parenchymal processes. A new series of X-ray treatments was given for swelling of lymph glands in the neck. — In the beginning of April 1938 fever again; temperature about 38° C. *Admitted to the Medical Clinic of the Serafimer Hospital on the 27/4 1938.* From status: slender build, very thin, weakly developed musculature. No cyanosis or dyspnea when resting; no edema. In the left axilla a couple of lymph glands the size of shell-almonds. Otherwise no palpable enlarged lymph glands. *Lungs: entire left half of the thorax bulged more markedly than the right. Considerable left-sided dullness, inhibited or very much weakened respiratory sound over the left lung.* Abdomen: the spleen was palpated three finger's breadths below arcus. The liver not palpable. Blood: hemoglobin 70 %, red blood corpuscles 3 mill/mm<sup>3</sup>. White blood corpuscles 6,500. Differential count: neutrophile 73 %, eosinophile 1 %, basophile 1 %, lymphocytes 21 %, monocytes 4 %. Sedimentation rate 123 mm/hour. *Mantoux negative* with 0.1 mgm tuberculin. *Thoracocentesis* on the 2/5 1938, when 2,800 ml of *clear, light yellow exudate* was drained off. *Thoracoscopy* showed the lung to be lying strongly collapsed against the hilus. It was atelectatic and greyish blue in colour. *Pleura parietalis* was *not particularly reddened* but showed slight vascular injection. On the lowest part of the inferior lobe were observable on the surface of the lung some yellow-white nodules ranging up to the size of a pea. *On the diaphragm, within the region of the cupola and adjacent parts were observed yellow-white, tumour-like formations ranging from the size of a hemp-seed to that of a walnut.* No ulceration. No fibrin in the pleura. The pleural exudate contained 4 % albumen. Of the cells in the exudate 85 % were lymphocytes and 15 % polynuclear cells, of which 4 % were eosinophile leucocytes. Preparation according to *Wihman's method of enrichment* did not enable any definite cytological diagnosis; the amount of fibrin was slight, the majority of cells consisted of leucocytes; there were in addition a moderate number of partly degenerated endothelial cells, no giant cells. X-ray on the 3/5 1938: left-sided pneumothorax with exudate basally and with almost complete collapse of the lung. In the central part of the collapsed lung a patchy density. No pathological change in the right lung. — On the 12/5 a further 2,000 ml of clear exudate was drained off, and on the 24/5 2,000 more ml. After this the *tumour-like formation in the thorax* was

submitted to X-ray treatment. On the 6/6 1938, 1,100 ml of exudate was drained off and on the 20/6 1,600 ml. On the 18/7 1,250 ml of clear exudate was drained off. The sedimentation rate was then 55 mm/hour. After this no more exudate was formed. Guinea-pig tests on the pleural exudate gave on four different occasions negative results for tuberculosis. After some time during which the patient felt relatively well there was a worsening. *Mors* at home in the spring of 1939 without any signs of renewed pleural exudation having appeared.

*Case 2. Nurse, born 1909.* No tuberculosis or cancer in the family. In June 1939 began to be troubled with stitch in the left side, dry cough and shortness of breath on exertion. No fever. Admitted to the Medical Clinic of the Serafimer Hospital on the 31/7 1939. From status: Afebrile. General condition good. Well-fleshed. Superficial lymph glands not pathologically enlarged. Abdomen: liver and spleen not palpable. Lungs: on physical examination showed signs of left-sided pleuritis with considerable exudation. Blood: hemoglobin 98 %. Red blood corpuscles 4.8 mill/mm<sup>3</sup>. White blood corpuscles 5,800. Differential count: neutrophile 68 %, eosinophile 2 %, monocytes 6 %, lymphocytes 24 %. Sedimentation rate 4 mm/hour. Mantoux negative with 3 mgm tuberculin. Thoracocentesis: 2,800 ml clear light yellow fluid was drained off. Thereafter thoracoscopy: pleura parietalis slightly reddened. No characteristic tuberculous nodules observed anywhere; no fibrin in the pleural cavity. The lung was strongly collapsed and grey-blue in colour. On the surface of the posterior part of the inferior lobe, but also on adjacent parts of the superior lobe near the incisure the lung was seen to be infiltrated by grey-white, nodular, tumour-like formations; no ulcerative processes. Specific weight of the exudate: 1.018. The predominating cells were eosinophile leucocytes. In a preparation according to Wihman's method of enrichment some sparsely occurring inflammatory cell elements were observed, as well as a few larger cells occurring singly or in small groups, the latter by all appearances swollen and degenerated endothelial cells; no definitely pathological cells. Guinea-pig tests carried out on the exudate gave on three different occasions negative results for tuberculosis. As malign tumour was suspected the left part of the thorax was subjected to X-ray treatment. In this connection, a density in the left lung that was observable after the centesis diminished considerably in size. The tendency to exudation also decreased, so that only one further drainage, when 2,000 ml was removed, was required. — In June 1940 the patient noticed a swelling in front of the sternum. In August 1940 a firm swelling with a diameter of about 5 cm, movable against the skin but fixed below and only slightly tender, was palpated over the sternum 3—4 cm from jugulum. Corresponding hereto, X-ray examination showed an irregular clearer area in the upper part of corpus sterni. The tissue «worm» obtained on puncture showed an inflammatory picture with numerous polynuclear leucocytes and epithelioid cells but no giant or tumour cells, and no necroses. The staining of the section to show tubercle bacilli gave a negative result. The swelling diminished after X-ray treatment. — In October 1940 the patient complained of an ache in the left axilla; and for the first time an enlarged lymph gland the size of

*a shell-almond was palpated. This was extirpated on the 2/11 1940. Microscopically it showed only in small areas a more or less intact lymph gland structure. Otherwise the lymphatic tissue was markedly changed, showing the cell-content characteristic of lymphogranulomatosis: swollen reticular cells, numerous giant cells of Sternberg's type, plasma cells and a large number of eosinophile cells. On the 16/11 1940 X-ray examination revealed a moderate lymph gland enlargement in the right lung hilus. Patient's general condition still good. Sedimentation test 15 mm/hour. Was given further X-ray treatment in 1940 and 1941. — In February 1942 the patient fell ill, with high fever, aching in the joints of the hand, elbow, foot and knee, and with reddish violet, tender efflorescences the size of a penny on the extensor parts of the lower arms and the legs below the knee (erythema nodosum). Mantoux positive with 1 mgm tuberculin. Sedimentation rate 59 mm/hour. X-ray of the lungs still showed glandular enlargement in the right hilus. In December 1942 the patient's general condition was still good. In left fossa supraclavicularis and right axilla were palpated glands the size of a butter-bean. Sedimentation rate 13 mm/hour. Was given a new series of X-ray treatments. — In February 1944 the general condition of the patient was still excellent. Weight 75 kg. On the right side of the neck there was a firm gland the size of a butter-bean, and in the right axilla a conglomerate of glands the size of a walnut. Otherwise no pathologically enlarged, superficial lymph glands. Sedimentation rate 17 mm/hour. Was given a new series of X-ray treatments.*

### Discussion.

*The two cases described above have certain features in common. The exudation developed rather stealthily, without any very pronounced effect on the general condition in the form of rise of temperature, feeling of stitch etc. The exudates were clear, and light yellow in colour. They had the same appearance as that generally characterizing exudative tuberculous pleuritis. No definitely pathological cell elements were demonstrable in the exudates; but in the one case the eosinophile cells predominated while in the other there were 4 % eosinophile cells. In both cases fresh quantities of fluid were formed after the first centesis. Thus in the one case 4 litres and in the other nearly 11 litres were removed before the exudation finally stopped in connection with the commencement of X-ray treatment. Both patients gave negative tuberculin results, and repeated guinea-pig tests carried out on the exudates were negative for tuberculosis.*

*In one important respect there was a fundamental difference between the two cases. While in the second patient the pleuritis arose in a previously completely healthy person, in the first case it occurred in*

a patient who 1 ½ years earlier had been diagnosed as a case of lymphogranulomatosis in connection with the histological examination of excised lymph gland. While in the case of the latter patient the connection of the pleuritis with the primary disease was a priori clear, in the former case the continuous pleural exudation in an afebrile patient with normal sedimentation rate constituted a difficult diagnostic problem. Nor was it possible to make a definite diagnosis until more than a year had elapsed, when an enlarged lymph gland that appeared in the course of the further development of the disease was extirpated and subjected to microscopic examination.

The second case illustrates how an extraglandular lymphogranulomatosis occurs as an at least apparently independent clinical disease with symptoms from the pleura. From this viewpoint alone a fairly detailed casuistic mention is justified, since a pleural reaction of this kind has to the best of my knowledge not previously been described as the first clinical manifestation in a case of lymphogranulomatosis.

Of particular interest are the diagnostic possibilities offered by thoracoscopy in the two cases. In the inspection of the pleural cavities performed in connection with the centeses carried out it was thoracoscopically possible to exclude tuberculosis as a cause of the pleuritis. Pleura parietalis was only slightly reddened, no typical tuberculous nodules were to be observed, in the pleural cavity it was not possible to demonstrate either fibrin patches on the surface of the lung or fibrin sails between the lung and the thoracic wall. The changes visible in the thoracoscope were localized to limited regions on the pleural cavity. In the first patient the changes were chiefly demonstrable on pleura diaphragmatica, where yellow-white, tumour-like formations varying in size from that of a hemp-seed to that of a walnut were observed. In the second case there was on pleura visceralis, especially in the back part of the inferior lobe, a similar, tumour-like infiltration, though here it was more a matter of small nodules. In the case of the latter patient one must take into account the fact that the pleura had been involved in the process from lymphogranulomatosis foci in the lung. In the first case, on the other hand, where it was chiefly the diaphragm that was the seat of the change, it is possible that the disease had reached the pleura from organs of the abdomen. These two patients thus

represent pleural lymphogranulomatosis of two of the types described by Versé and stated by him to be characterized in the one case by small nodular formations and in the other by larger, knottier changes.

The *macroscopic appearance* of the changes in the pleura observed in both these cases was such that, especially in consideration of the greater frequency of the malign tumours, *there was in the first place reason to suspect cancer*. In the second patient, where the pleurally demonstrable change was at first the only manifestation of disease, the cancer diagnosis was in the earlier stage of the illness regarded as probably correct. Certainly, the large number of eosinophile cells in the pleural exudate might in this case have drawn attention to the possibility of lymphogranulomatosis; but no cell elements that could definitely support this diagnosis were found.

A valuable addition to the *cytological diagnostic possibilities* was provided by *Wihman's method of enrichment*, where the chances of demonstrating typical cells in histological preparations from the sectioned exudates are considerably greater than in direct preparations. The giant cells typical for lymphogranulomatosis were not, however, found in enriched preparations from either of the cases. The slight amount of fibrin, the moderate number of endothelial cells and the large number of leucocytes constituted a definite contra-indication as regards tuberculosis, and tended to strengthen the suspicion of tumour. Cytologically, however, both the cases must be referred to the group of rare forms of pleural discharges in which the examination of the exudate does not permit of a sure diagnosis. But one cannot accept as generally valid the view put forward in Ratkóczy's monograph, that the microscopic examination of the exudate does not lead to any characteristic finds.

A diagnostic method that in direct connection with the draining of the pleural exudate enables one to form a definitive opinion of the nature of the observed tumour formations is with the help of the thoracoscope to make a test excision in the pleural region manifesting morbid changes. If this had been done in the second case all doubt as to the real nature of the tumour-like pleural formation would soon have been dissipated.

The *treatment* of the changes in the pleura does not, of course, differ from the accepted therapy for other lymphogranulomatosis

localizations. The possibilities of ray treatment were exploited in both cases. The effect was extremely favourable on the pleural symptom complex. *The recidivating exudation began gradually and progressively to recede.* The interval between the drainings became longer, until centeses became superfluous. During the later stage of the disease there were in neither of the two cases any signs indicative of a return of the pleural process. The period during which the second case was under observation was about 5 years after the disappearance of the pleural symptom complex.

### Summary.

An account is given of two cases of lymphogranulomatosis maligna, in which symptoms from the pleura dominated the clinical picture during one phase of the disease. A detailed account is in the one case motivated, if for no other reason, by the fact that as far as is known to the author symptoms from the pleura have not previously been described as the first clinical manifestation of «primary» extraglandular lymphogranulomatosis. In both cases the pleuritis showed agreement with the reaction of the pleura in malign tumour, especially in the circumstance that in connection with the centeses carried out the exudation showed a strong tendency to rapid recidivation. Also thoracoscopically the picture agreed with the changes that are generally observed in cases of malign tumour in the pleura. The diagnostic possibilities presented by thoracoscopy have probably not been sufficiently taken into account in the past. Cytologic examination, especially of histological preparations of the exudate produced with methods of enrichment, and test excisions undertaken in the changed pleural region with the help of a thoracoscope, are also methods of investigation that should not be left untried in cases in which tumour-like pleural changes constitute difficultly interpretable diagnostic problems.

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## On Pre-excitation.

(WPW syndrome).

By

LEO NORO.

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### Introduction.

*Pre-excitation* (Öhnell), previously known as the *Bundle of Kent* or *Paladino-Kent*, or the syndrome of *Wolff-Parkinson-White* (WPW), has till now been considered a rare phenomenon in the electrocardiography, as until the end of 1944 only 300 such cases were published in the literature of the world. Among them were Rissanen's 4 cases from Finland in 1939. The Swede Öhnell's thorough investigation during the last years shows, however, that the phenomenon is not uncommon, which is proved by the fact that he found 70 cases of pre-excitation, while the Danes Mortensen, Nielsen and Eskildsen discovered 45 cases in the same year. Öhnell mentions that e.g. among 300 electrocardiograms taken monthly at the Karolinska sjukhuset an average of one pre-excitation case was noted. This figure, however, seems very high compared with the statistics of frequency worked out by Mortensen and others. This may be explained by the fact that Öhnell includes among pre-excitation cases also such ECG:s which do not correspond with the earlier typical WPW picture and among which, for instance, types that have generally been called extrasystoles emanating from the upper part of the av-node are found. Every medical specialist having encountered now and then such types of ECG naturally understands that this phenomenon is not uncommon.

I shall not discuss the electrocardiographic and clinical picture of pre-excitation in this connection as Öhnell, Mortensen and others have recently given a thorough explanation thereof in the columns of this paper.

In the following I shall describe my own case as new aspects have arisen which justify this publication.

### Case report.

*Patient:* A peasant, aged 31, infantry soldier in front service.

*Diagn.:* Myocarditis. WPW syndrome.

In medical ward 3. 4.—10. 11. 44. Discharged improved.

#### Anamnesis.

*Heredity:* Father died of heart disease at the age of 70. Sister suffers from heart disease, the nature of which is unknown to the patient.

*Previous illnesses:* 9 years ago polyarthritis. 4 years ago gonorrhoea. In January 1944 an acute enteritis on account of which two weeks' treatment in hospital. In February broncho-pneumonia, two weeks in hospital. Since January pains in the right wrist, in which swelling appeared in April. Again sent to hospital, diagnosis: polyarthritis ac. Complications while in hospital, angina and at the end of April sudden inflammation of middle ear which was noted cured on the 2. 5. 44 in the records. Somewhat later a sinusitis appeared, cured 15. 5. 44. Sedimentation reaction, which at the end of February had been 5 mm/h, was on April 1st, when admitted into hospital, 19 mm/h and rose 14. 4. 44 to 120, then sinking to 11/32 mm in  $\frac{1}{2}$  h. on 18. 5. 44 when the first heart symptoms appeared. *Thus multilateral infectious anamnesis.*

*Anamnesis of the heart:* The patient had never felt any pains in his heart before. On 18. 5. 44, when leaving hospital on convalescence leave, the patient's heart suddenly began to beat when carrying heavy equipment. He felt stitches in the region of his heart and a dizziness in his head. The attack lasted for about 10 min. On the way home from the train the pains were renewed. When walking he felt a pressure close to his heart and he was short of breath. At the same time he felt dizzy and a headache came on. The patient had to stop and rest very frequently on account of the pressure on his heart. At rest the pains were absent but when the patient started work again after a week in bed the pains returned and he even fainted once in the fields. The pains were probably due to a myocarditis that had set in some time before.

#### Status.

Immediately after returning from leave, on 10. 6. 44 (that is 3 weeks after heart symptoms had set in) the patient was sent to a medical ward to be examined. His state was as follows:

*St. univers.*: General condition good. Subcutaneous tissue not reduced. Glandula thyreoidea ordinary. Tenderness in right wrist, no crepitation, no swelling.

*App. nerv.* Mental state: very sensitive. Nervous and restless. Dermography slow. No tremor. Skin, achilles and patellar reflexes ordinary, symmetric. The pupils equally large, round, middle sized, reacting to light and convergency.

*App. resp.*: nothing special.

*App. dig.*: One carious tooth. In throat and tonsils no signs of inflammation. Ewald's meal 110 cm<sup>3</sup> badly digested. HCl: —, TA: 34.

*App. circ.*: Pulse regular, not celer, not tardus, middle sized: Frequency 70/min. Arrhythmia respiratoria. Blood pressure 150/100 mm Hg. Heart tones rather strong and sonorous. No accentuations in apex a systolic murmur. Fluoroscopy: nothing special.

Sedimentation rate: 8 mm/h. WaR: —, Kahn: —, Kristensen: —.

In blood slight removal to left only posit. finding (staffnuclear leucocytes 6 %).

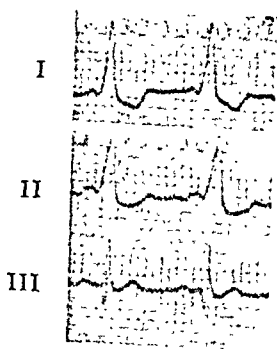
Blood sugar: 0.080 mg %.

Urine: Nothing special. Faeces: nothing special.

ECG 10. 6. 44: see picture 1.

### Picture 1.

#### First electrocardiogram.



Rhythm regular. Frequency 100/m.

PQ<sub>I</sub>: 0.07 sec. QRS<sub>I</sub>: 0.12 sec. R<sub>I</sub>: 1.7 mV

PQ<sub>II</sub>: 0.10 sec. QRS<sub>II</sub>: 0.12 sec. R<sub>II</sub>: 1.8 mV

PQ<sub>III</sub>: 0.16 sec. QRS<sub>III</sub>: 0.07 sec. R<sub>III</sub>: 1.1—1.2 mV

ST<sub>I—II</sub>: negative, T<sub>I</sub>: isoelectr., T<sub>II—III</sub>: posit.

In R<sub>I—II</sub> a distinct indentation in the rise. Initial slope: 8 mV/sec. (According to Öhnell's classification the case should belong to Pre-ex Model 1944.)

*Summary:* anamnesis and auscultatorial finding indicate myocarditis, and in addition to this a slight hypertonia and a sensitiveness in the vegetative system.

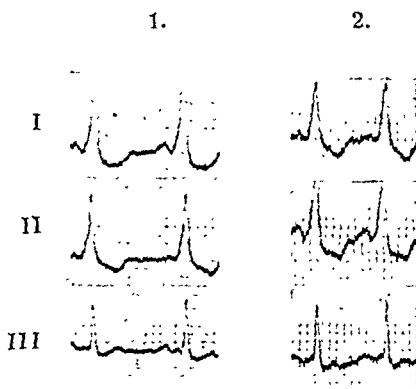
*Decursus morbi:*

The patient was treated first with acid. phaenylaethylbarb.  $0.03 \times 3$ . In ECG:s taken during a month the same changes as in the first ECG always appeared even if small changes in the shape of pre-ex. were observed. (Picture 2).

**Picture 2.**

*Changes in picture of pre-excitation.*

(1. — 13. 6. 44; 2. — 26. 6. 44.)



1. Rhythm regular. Frequency 100/min.

$PQ_I$ : 0.07 sec.  $QRS_I$ : 0.11  $R_I$ : 1.5—1.6 mV

$PQ_{II}$ : 0.11 sec.  $QRS_{II}$ : 0.11  $R_{II}$ : 2.0 mV

$PQ_{III}$ : 0.10 sec.  $QRS_{III}$ : 0.11  $R_{III}$ : 1.1—1.2 mV

Initial slope 8 mV/sec. Pre-ex appears for the first time in ECG also in III lead.

2. Rhythm regular. Frequency 120/min.

$PQ_I$ : 0.07 sec.  $QRS_I$ : 0.10—0.11 sec.  $R_I$ : 1.4—1.5 mV

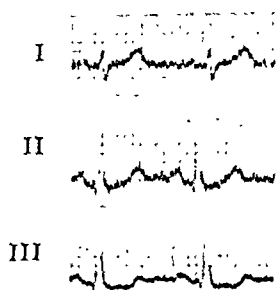
$PQ_{II}$ : 0.11 sec.  $QRS_{II}$ : 0.12—0.13 sec.  $R_{II}$ : has not been measured

$PQ_{III}$ : sec. 0.13  $QRS_{III}$ : 0.10—0.11 sec.  $R_{III}$ : 1.5 mV

Initial slope in I lead 12 mV/sec., II lead 2—8 mV/sec., III lead 2—4 mV/sec. Thus the variation in the same lead is remarkable.

Not until the elapse of 1 ½ month: is an electrocardiogram received in which no pre-excitation appears. (Picture 3).

## Picture 3.

*No pre-excitation in ECG.*

Rhythm regular. Frequency 100/min.

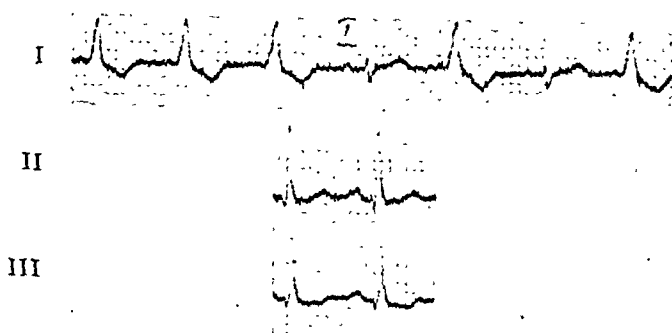
$PQ_{I-II-III}$ : 0.15 sec.  $QRS_I$ : 0.05 sec.,  $QRS_{II-III}$ : 0.06 sec.,  $R_I$ : 0.4 mV

$R_{II}$ : 2.1 mV

$R_{III}$ : 1.8 mV.

At the same time the appearance of the phenomenon is, however, still rather unstable. It may appear when taking the same ECG during different leads, and partly in the shape of a bigeminy. (Picture 4).

## Picture 4.

*Pre-excitation in I lead only.*

Rhythm regular. Pre-ex. appears in I lead in every beat, then in every second beat, the rhythm remaining regular. In II and III leads pre-ex. has disappeared. Compared with other pictures  $P_I$  is here small,  $PQ_I$ : 0.07 sec.,  $QRS_I$ : 0.10 sec.,  $R_I$  conspicuously lower: 1.0 mV. Thus when taking the ECG a normalization of the pre-ex. occurs after having passed through a bigeminy shape.

*Summarizing the above mentioned facts we may say that pre-ex. seems to be of a rather unstable nature, and may appear in ECG:s taken at different times, in various forms.*

During his stay in hospital the patient had no subjective symptoms. But when getting up, pains in the chest, around the region of the heart and a feeling of pressure set in, specially when straining himself. Signs of heart insufficiency were not observed. The blood pressure varied between 150/100—170/110 mm Hg. The sedimentation rate remained all the time under 7 mm/h. After about two months the systolic murmur had disappeared. Renewed fluoroscopic examinations brought to light (even after 3 months) signs indicating myocarditis.

### *Experiments on appearance and disappearance of pre-excitation.*

Appearance and disappearance in various ways of pre-ex. have been recorded in literature (Cf. Lepeschkin, Öhnell). It has been caused to *disappear* by exercise causing acceleration of the heart frequency, amyl-nitrite, vasocordin, atropine, carotis and bulbus pressure, quinidine, after thyreoidectomy and tonsillectomy, lying on the left side, by strophanthine, digitalis, and spontaneously, during fever, when standing up and while holding the breath. But it has been caused to appear also after exercise, by carotic pressure and while breathing deeply. According to some observations exercise did not have any effect.

## **My personal observations.**

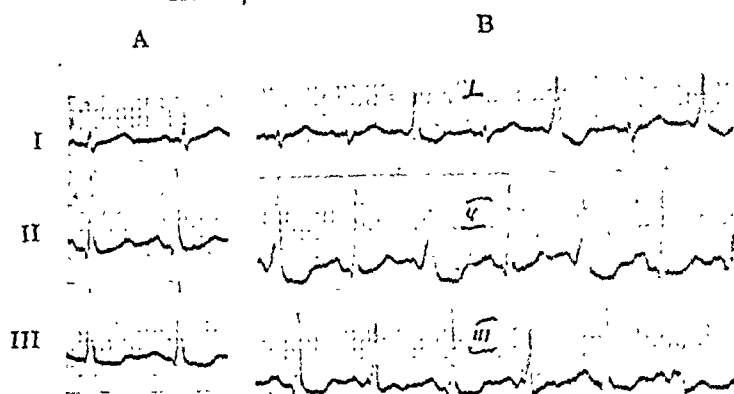
### *1. Spontaneous appearance and disappearance.*

It has often been observed that pre-ex. appeared in one or two leads, generally in I and II, and disappeared already while taking the third lead (See pictures 2 and 4).

### *2. Exercise test.*

Three tests have been undertaken at different times. Kneebending 10—15 times was used as exercise. In the first test pre-ex. appeared immediately after exercise in the shape of bigeminy and disappeared again after 5 min. (Picture 5). In the second test it appeared similarly but disappeared after 3 min. and in the third test it appeared only in I lead and disappeared when II lead was being taken.

## Picture 5.

*Exercise test.*A. *Before exercise.* B. *After exercise.*

Immediately after exercise pre-ex. appears during I lead in which three different beats are seen. In the II lead the attention is directed to the double indentation of P which has not appeared previously. The rhythm is regular. Frequency 120/min.

3. *Positions.*

Pre-ex. does not disappear when resting on the left or the right side. After standing up PQ time remains unchanged but QRS is shortened from 0.13 sec. to 0.10 sec.

4. *Bulbus pressure.*

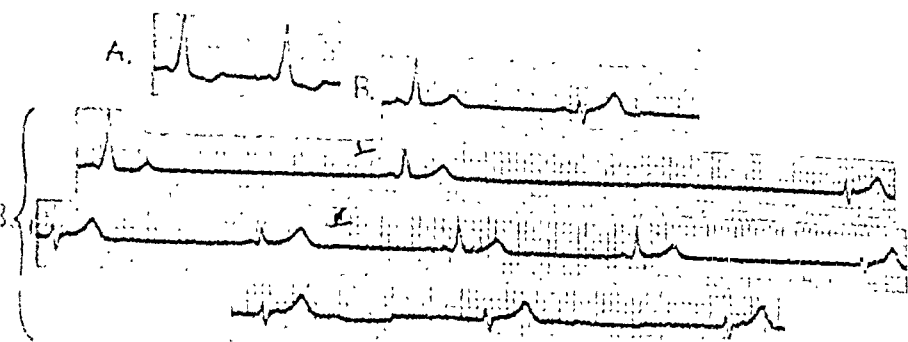
In picture 6 pre-ex. disappears during pressure.

## Picture 6.

*Bulbus pressure.*A. *Before pressure.* B. *During pressure.*

In the picture the shortening of QRS is seen while the frequency is abating. In between comes a normal beat but after that still 2 pre-ex. beats, after which there is a pause of 2.6 seconds. The sinus rhythm now disappears, but pre-ex. beats still appear until they disappear altogether. P is





(I Lead)

seen immediately after S in the beats. The R—R period varies slightly: 1.85—1.30 sec. A lower nodus rhythm is thus in question.

### 5. Medicines.

The obvious effect of the bulbus pressure exciting the vagus gave rise to experiments with medicines that are known to influence the vegetative nervous system. The following medicines were used, the effect of which are mentioned within brackets: 1) adrenaline (excites sympathetic), 2) ergotamine (calms sympathetic), 3) acetylcholine (excites vagus) and 4) atropine (calms vagus).

1). *Adrenaline* 0.3 cm<sup>3</sup> (1: 1000) was administered intravenously (Picture 7).

#### Picture 7.

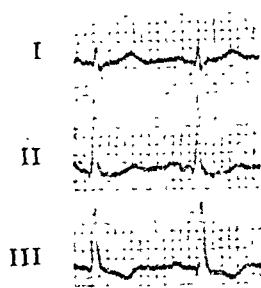
##### *Adrenaline test.*

##### *A. Before injections. B. After injections.*

In the ECG taken immediately after the injection pre-ex. beats conspicuously differing in shape from the previous beats are noticed. The shapes observed in the first beat are still comparable with those noticed during bulbus pressure (see picture 6). During III lead they change gradually in the stative direction. Appearances are similar in ECG taken 1 ½ min. after injection. Attention is especially directed to shapes in II lead in which there is a wide QRS (0.17 sec.) and a deep T. After 8 minutes ECG is again normal.

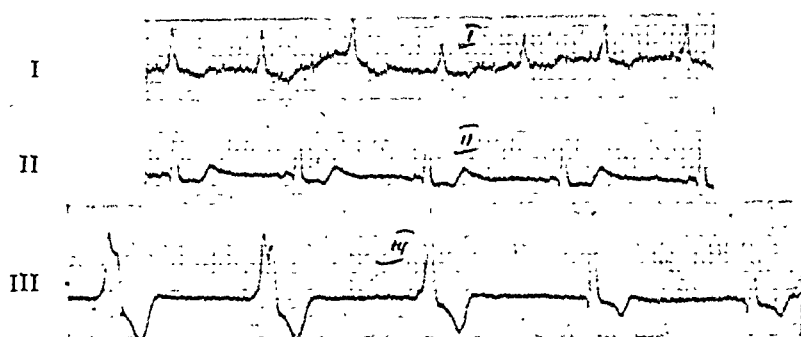
In a renewed test in which the patient receives subcutaneously 0.5 cm<sup>3</sup> adrenaline, the pre-ex. that before the test had appeared in the shape of a bigeminy remained unchanged for 5 min. but has disappeared in ECG taken after 15 min.

A

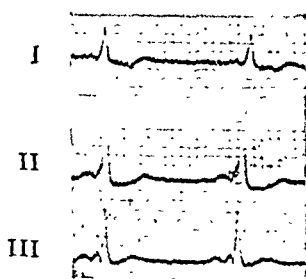


B

Immediately



After 1½ min.



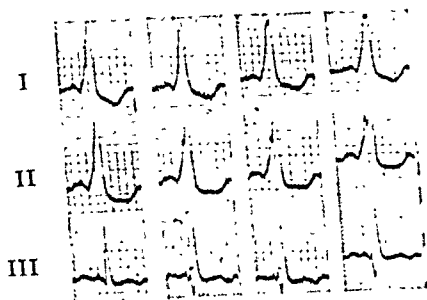
2) *Ergotamine* (Gynergen, Sandoz) 0.00025 g was administered intravenously. (Picture 8).

### Picture 8.

*Ergotamine test.*

A. *Before injection.* B. *After injection.*

Pre-ex. appears in every beat before the test. After one min.  $T_{I-II}$  becomes lower, in the II lead the barb of the rising part becomes more



distinct and Q becomes deeper in III lead. After 3 min. the barb has become still more distinct and  $Q_{III}$  deeper. After 10 min.  $Q_{III}$  deepens still a little. This means that normalization does not occur after all. During the test the blood pressure decreased from 170/100 to 140/100 mm Hg. Nausea and headache were subjective pains felt during the test. The pulse frequency slowed down from 100 to 80. Thus a paradoxical effect of ergotamine is here in question. (Cf. Nordenfelt).

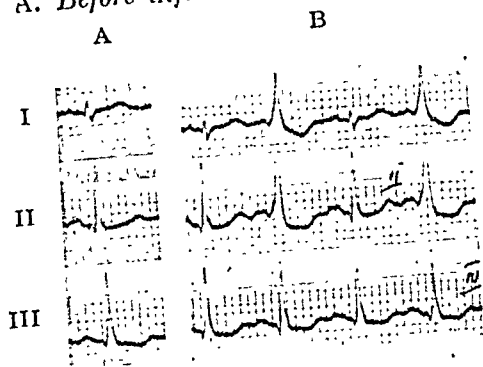
3) *Acetylcholine* (La Roche) injected intramuscularly in dose of 0.1 g. ECG taken 6 and 17 min. later did not show any clear changes.

4) *Atropine*, 0.0005 g was administered intravenously. (Picture 9).

### Picture 9.

#### *Atropine test.*

A. Before injection. B. After injection.



Pre-ex. does not occur before test. In ECG taken 3 min. after injection pre-ex. appears in every second beat, but disappears again 6 min. later.

In a second test, in which pre-ex. occurred in every beat before the test, an injection of 0.0007 g atropine intravenously caused no changes in ECG.

5) *Calcium chloride*, 10 ml (10 %) injected intravenously. Before test no pre-ex. No changes to be observed.

6) *Quinidine* is administered in tablets ( $0.1 \times 3$ ) during two weeks. During cure pre-ex. cannot be brought out but appears again one week after treatment has been stopped.

7) *Bellergal* (Sandoz), one tablet 4 times a day. After 2 and 4 days pre-ex. does not appear in ECG and the patient declares that he has no more pains and feels quite well.

*Summarizing* the above-recorded tests we find that, at least in this case, the phenomenon has been very unstable, appearing and disappearing spontaneously in the different leads of ECG pictures. In three exercise tests it appeared regularly although the duration differed from about 20 sec. to 5 min. Different positions were not found to affect it. It was caused to disappear by bulbus pressure. The most conspicuous effects seem to have been obtained by adrenaline, which caused it to appear immediately after an intravenous injection, whereas ergotamine and acetylcholine did not cause a disappearance. Contrary to previous observations, pre-ex. could be caused to appear by atropine but not to disappear. It could not be produced by  $\text{CaCl}_2$ . Quinidine and Bellergal taken per os caused a disappearance.

### Discussion.

Both myocarditis and the sensitiveness of the vegetative nervous system seem to have a part in the phenomenon. A fact that cannot be ignored is that as no ECG was taken before the appearance of myocarditis, the possibility remains, of course, that the patient had suffered from pre-ex. earlier, although no subjective pains appeared. Is the pre-ex. in this case caused by myocarditis or is it a find at the side of or in connection therewith — that remains unsolved so far. Anyhow, it appeared as more stable at the beginning of the myocarditis than later on.

The experiments recorded above have all the same shown that the sympaticus-parasympaticus effects seem to be remarkable in the phenomenon. The influence of Bulbus pressure and Bellergal

on the one hand, and of adrenaline and atropine on the other, in the appearance and disappearance of pre-ex. have been obvious in my case. No results were, however, attained with ergotamine and acetylcholine.

Although conceptions of the mechanism of the effect of the sympathetic and the vagus concerning the activity of the specific muscle complex of the heart are still confused in many points, it may, however, be considered fairly certain that the sympathetic possesses a promoting influence on all its qualities, i. e. chrono-, bathmo-, dromo-, and inotropic qualities, whereas the vagus has a checking influence. Still, it must be said that the vegetative nervous system forms a firm complex in which e. g. the above mentioned medicines may influence both components (Cf. Nordenfelt). The bulbus pressure is generally considered to be the excitator of the vagus. In my case the effect of it corresponds with previous observations (Öhnell, Lepeschkin): it causes the disappearance of pre-ex. Special notice must be attached to the shortening of QRS (Picture 6) during pressure and the simultaneous rise of T. Only one normal shape can be produced in between, but instead a lower nodal rhythm appears in which beat an exceptionally high T-wave is noticed. What is the explanation of this phenomenon? I cannot here enter upon the various hypotheses that have been brought forward as to the origin of pre-ex. Öhnell has given a good and concentrated report on them in his last publication. In my own case I consider the following explanation to be acceptable: a new excitation centre has arisen in the auricle perinodally or in the upper nodal, which causes a shortening of PQ time. The excitation moves normally more quickly in the His Bundle and Tawara Branch and the ECG shows a picture resembling an arborization block (see picture 1, I and II beat). While the vagus is being excited (see picture 6) an excitation of the branch is gradually produced and ECG approaches the normal. In one area the secondary centre of excitation capacity ceases and is replaced for a moment by a sinus beat the characteristic of which is a seemingly normal beat. The situation still being rather unstable, the (para-)nodal rhythm is allowed to dominate for a moment until, the bulbus pressure continuing, a lower nodal rhythm replaces it, in which the P-wave appears after S which, again, may be explained as a sign of an excitation in the ventricles retrogradically caused by the nodus, although it is positive as well.

Thus, we may in this case consider the appearance of pre-ex. picture due to an excitation centre in the perinodal or upper part of the nodus which has taken the place of the sinus node and that the excitation moves more quickly in the one half of the Bundle of His and in the Tawara Branch. Probably the myocarditis has, just in this case, been a factor causing this phenomenon. On the other hand we may think that the myocarditis, while injuring the one Tawara branch, may, on account of the retardation of the excitation, create a typical »Verspätung» picture. But if this were the case, why should the excitation of the vagus, which should retard the excitation still further, bring about a normalization?

It is also possible that in the other side of the a-v-system exhaustion would appear, which would cause the changes in the ventricular part. The equal changes in QT are to be found in nodal extrasystolia.

The increased sympathetic tonus seems to cause a sensitive functioning of the centre as shown in the adrenaline test. We know that the influence of adrenaline on ECG (Vesa, Hochrein, Lepeschkin) causes increased alterations in the origin and appearance of excitation which then appear, for instance, as auricular and ventricular extrasystoles, changes of sinus rhythm into nodal rhythm (note the effect of bulbus pressure in my case), and the shortening of PQ and QRS. In my adrenaline test (picture ) we observe immediately after the injection, in lead I, when the frequency is fast (120/min.), lesser alterations in the ventricular complex than later on when the frequency is only 60/min and when the changes in QRS are particularly noticeable. They may surely be due to an already beginning relative coronarial insufficiency caused by adrenaline (Vesa), in which case they are also affected by the retardation of the excitatory appearance in the ventricles. According to Vesa the adrenaline first causes disturbances in the appearance and origin of the excitation and secondly symptoms of coronarial insufficiency.

The fact that the increased sympathetic tonus — this time by indirectly lowering the tonus of the vagus — produces the phenomenon, is a kind of evidence of the effect of atropine. Possibilities of spontaneous appearance should here be taken into consideration.

The favourable effect of Bellergal in my case must probably be explained by the fact that it generally effects favourably the disturbances in the vegetative nervous system.

### Summary.

The author introduces a case of pre-excitation in a man of 31 years, in whom the typical ECG changes were noted in connection with inflammation of the heart muscle (Picture 1). In addition, the patient showed signs indicating unstableness in the vegetative nerves, and a slight hypertonia. In ECG pre-excitation appeared in different beats somewhat varying in shape (Picture 2) and either in every beat or in the shape of bigeminy (Picture 3). The phenomenon was *unstable* and appeared or disappeared *spontaneously* (Picture 4). Different positions did not affect it. Pre-excitation *appeared* in three tests immediately *after exercise* and lasted from 20 seconds to 5 minutes (Picture 5). *Bulbus* pressure caused a *disappearance* and nodal rhythm appeared instead (Picture 6). Pre-excitation was caused to *appear* by *adrenaline* (Picture 7) and contrary to former observations also by *atropine* (Picture 8). *Quinidine* and *Bellergal* administered per os caused a *disappearance*. *Acetylcolin* and  $\text{CaCl}_2$  did *not affect* the phenomenon.

The etiology and pathogenesis of the phenomenon have been discussed.

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From the Department of Physiology and the Medical Clinic, University of Lund, Sweden.

## The effect on muscular temperature produced by cooling normal and ultraviolet radiated skin.

By

H. I. BING, ARNE CARLSTEN and SV. CHRISTIANSEN.

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According to Buchthal and Lindhard (1944) the temperature of striated muscles in human beings varies in different muscles from  $32.8^{\circ}\text{C}$ — $36.8^{\circ}\text{C}$ .

If a piece of meat is for several hours heated in an incubator at  $37^{\circ}\text{C}$  and subsequently placed at room temperature, the temperature of the meat, measured at 3 cm beneath its surface, decreases very quickly. In one experiment the fall in temperature amounted to  $3.4^{\circ}\text{C}$  in 17 minutes.

In men and homoiothermic animals the body temperature is kept constant by means of a special regulating mechanism.

The temperature of a resting muscle in the intact homoiothermic organism is prevented from dropping to the level of its surroundings by:

1. the heat derived from the metabolism of the muscles and the blood circulating through the muscular vessels, and
2. the isolatory power of the integuments surrounding the muscles.

It may therefore be assumed that it is the heat derived from the blood flowing through the muscles at rest, which besides the muscle metabolism, is of importance for maintaining muscular temperature. The covering integuments act both as a passive insulator and



as a sort of heated mantle, due to the blood flowing through skin and subcutaneous tissue. If one or more of the elements in the system fails, it may cause cooling of the muscles. Whether the cooling of the muscles alone, or in combination with other factors, may cause symptoms of different kinds and in some cases the development of real disease, is still a matter of conjecture. It is nevertheless a fact that in some cases acute discomfort and even disease may follow local cooling of moderate intensity.

Hence it may be of interest to study the mechanism of the cooling reaction in the muscle under various conditions. An investigation of the possible existence of a defence mechanism against cold would seem to be of special interest.

Besides the work of Buchthal and Lindhard, Lipross (1942) has published a rather extensive article on the influence of various kinds of physical therapy on tissue temperature. In some cases he has measured the muscle temperature after the subject had been exposed to different kinds of physical treatments. Although the work comprises some interesting observations, it is not possible to draw general conclusions from it, as the greater part of it is based on a few single observations.

In a previous paper Bing (1943) has published measurements of muscular temperatures before and after ultraviolet radiation of the covering skin. He found the muscular temperature higher for several days after one or more exposures to a mercury-quartz lamp. This can be explained either by assuming a reflectory dilatation of the muscular vessels beneath the irradiated skin or by a lowered heat conduction through the skin, depending upon some change in the properties of the skin not necessarily caused by erythema.

### Technique applied:

The muscular temperature was measured by means of a thermo-needle which is described by Buchthal and Lindhard (1944) in their paper cited above (2). The thermo-currents were recorded by means of a light-spot galvanometer, the sensitivity of which was  $3 \times 10^{-8}$  amp. per scale unit the inner resistance being 42 ohms.

The deflections of the galvanometer showed a linear variation with the temperature differences between the two solderings of the thermo-needle. The thermo-needle has been inserted into the muscle 3 cm deep. The subject was placed either sitting comfortably in a chair or laying on a

stretcher. In model experiments it could be demonstrated that temperature differences applied to the proximal end of the cannula produce an electromotive force of short duration. This error was overcome by insulating the cannula shaft by means of a celluloid mantle. Other experiments, some with subjects, have shown that heat conduction through the needle need not be considered. (This depends on the great heat capacity and relatively good heat conducting properties of the surrounding tissues. In air, which is a very poor conductor of heat and has a very small heat capacity compared to muscular tissue, heat conduction through the needle, however, influences the results considerably).

In some experiments the temperature of the skin covering the muscle investigated was measured by thermo-couples of the same kind as those used by M. Nielsen (1938).

### Experiments:

In most cases the temperature of the biceps brachii has been examined. In a small number of cases the temperature of the rectus femoris has been recorded. In most of our experiments we have observed a marked fall in muscular temperature during the first 15 minutes after inserting the needle. This confirms the observations of Buchthal and Lindhard (1944). The gradient is very steep during the first 15 minutes and from that time onwards the steepness decreases considerably and in some cases approximates constant values.

The decrease in muscular temperature is probably due to the diminished heat production and to the increased heat loss from the extremity examined which is at rest and bare during the whole experimental period. An increased heat loss due to conduction through the thermoneedle is as stated above highly improbable. Therefore the thermoelectrically recorded temperatures represent the time variations of intra-muscular temperature rather faithfully.

A piece of ice, and in some cases a small bag filled with ice, was used for cooling a skin area of usually  $4 \times 3$  cm. The skin was cooled for a period of 5 minutes. The temperature of the muscle was recorded at least 15 minutes before application of the ice. The recording was continued at least 20 minutes after the ice had been removed.

In 15 out of 54 subjects examined the muscular temperature was not recorded during the cooling period, it being impossible to record the temperature of the part of the muscle situated

exactly beneath the cooled area. In these 15 subjects the thermoneedle was removed and the ice placed directly over the spot where the needle had been inserted. After cooling the needle was reinserted in its old place. The observations showed that the fall in muscular temperature directly underneath the cooled area was much larger than in the adjacent parts of the muscle, which were not covered by the ice.

In 10 out of 23 subjects in which the temperature was recorded during the whole experiment, a rise amounting to  $0.5^{\circ}\text{C}$  was observed at the beginning of the cooling period. The temperature rise lasted in most cases not more than 3—4 minutes and was followed by a fall. (Fig. 1).

If cooling at moderate intensity was employed, the temperature rise during the first part of the cooling period could be observed in

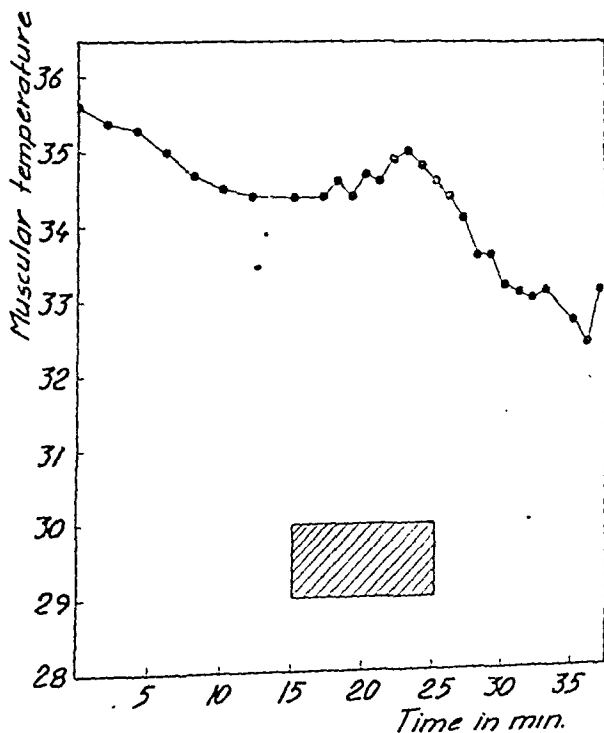



Fig. 1. Temperature of the right biceps is recorded. The skin covering the muscle is cooled with ice at .

all subjects examined. The cooling was produced by passing an air-current of  $22^{\circ}$  C over the skin. The air-current was produced by an electrolux vacuumcleaner.

During the whole experiment the temperature of the skin area cooled and of the underlying muscle was recorded.

The temperature of the skin dropped during 5 min. of passing the air-current from  $34.3^{\circ}$  C to  $24.2^{\circ}$ . Simultaneously the temperature of the underlying muscle rose  $0.3^{\circ}$  during the first 3 minutes of the passing of the air-current and after the first 3 minutes had passed a decrease of muscular temperature amounting to  $1^{\circ}$  C in 5 minutes was recorded.

If the circulation of the arm had been arrested before starting the air-current the muscular temperature did not rise at all. On the contrary a steady decline in muscular temperature could be observed from the moment the air-current was turned on and continued for 5 minutes after the air-current had been turned off.

In model experiments and measurements of the temperature of a piece of meat, no rise in temperature could be observed when blowing an air-current over the surface, technical errors thus being excluded.

The observed facts seem to fit the following explanation: The cooling of the skin produces at least during the first minutes an increased blood flow through the muscle (viz. while the skin temperature is falling the muscular temperature rises.) The reason for this phenomenon not being constantly seen when cooling with ice, may be that the amount of heat lost during the cooling period is so much larger than when applying an air-current, that the effect of a dilatation of the muscular vessels is obviated.

### Cooling reaction in subjects with normal, untreated skin.

We have recorded the temperature variations of the biceps brachii in 48 subjects.

In 6 persons an initial temperature rise was found. In all 48 subjects the temperature fell in 5—10 minutes after cooling had been discontinued. After the temperature had reached a minimum it again rose slowly and did not reach its original level until the close of the experiment, 20 minutes after the end of the cooling period.

1. *Temperatures recorded directly underneath the cooled surface. (discontinuous recording).*

The decline in muscular temperature caused by cooling varied widely. In some subjects it was only a few degrees C while in others a fall of more than  $10^{\circ}$  C was observed. The largest fall in temperature recorded was  $12.2^{\circ}$  C. The material showed a continuous transition from shallow and small decreases in temperature to steep and deep falls. The extremes being  $1.6^{\circ}$  C and  $12.2^{\circ}$  C respectively and the mean  $4.4^{\circ}$  C. The observations did not show any tendency of grouping themselves either in a group comprising only small temperature falls or in a group containing only deep and steep falls.

2. *Temperatures recorded during the whole observation period close to the cooled area (continuous recording).*

The biceps brachii of 23 persons were examined. The temperature curves recorded were distributed in a similar manner as in the observations previously cited, there being a continuous transition from no decrease in muscular temperature at all to a fall of  $5.7^{\circ}$  C. The mean was a decrease of  $2.3^{\circ}$  C.

It is not likely that this very marked variation in individual reaction to cold can be explained by differences in the thickness of the integuments covering the muscle examined. The muscle investigated was the biceps brachii, the skin covering of which is rather thin and with practically no subcutaneous fat in the region. The distance from the surface of the skin to the muscle hence can be supposed to be nearly constant in all the subjects examined.

To explain the differences by assuming individual differences in the metabolism of the resting muscle, seems rather unlikely. The most probable explanation appears to us to be a difference in the amount of blood flowing either through the muscle itself or through the covering skin and subcutaneous tissue. In the former case variation in the individual temperature reactions would be caused by individual variations of the amounts of heat transported to the muscles from the blood. In the latter case the insulating power of the integuments covering the muscle, would vary with the different amounts of blood flowing through the integumental vessels per second, and thus account for the individual variations in the cooling of the muscle.

*Observations on the mechanism of the cooling reaction in muscle as represented by muscular temperature.*

The question whether changes in the circulation of the muscle or in the bloodflow through the integuments account for the different course of the muscular temperatures, is elucidated by the observations described in the following pages.

The effect which results from the cooling of the skin covering a muscle is only local. When the temperatures of the other biceps or the m. brachioradialis on the same side were recorded simultaneously, no effect on the temperature of these muscles could be observed. (Fig. 2).

By recording simultaneously the temperature in different places in the same muscle it was found that the spread of the temperature fall from the part of the muscle directly beneath the ice rapidly decreased when the distance from the cooled area exceeded 2 cm.

In another series of experiments the effect upon the muscular temperature by obstructing the circulation to the muscle was compared to the effect of cooling the symmetric muscle. It was

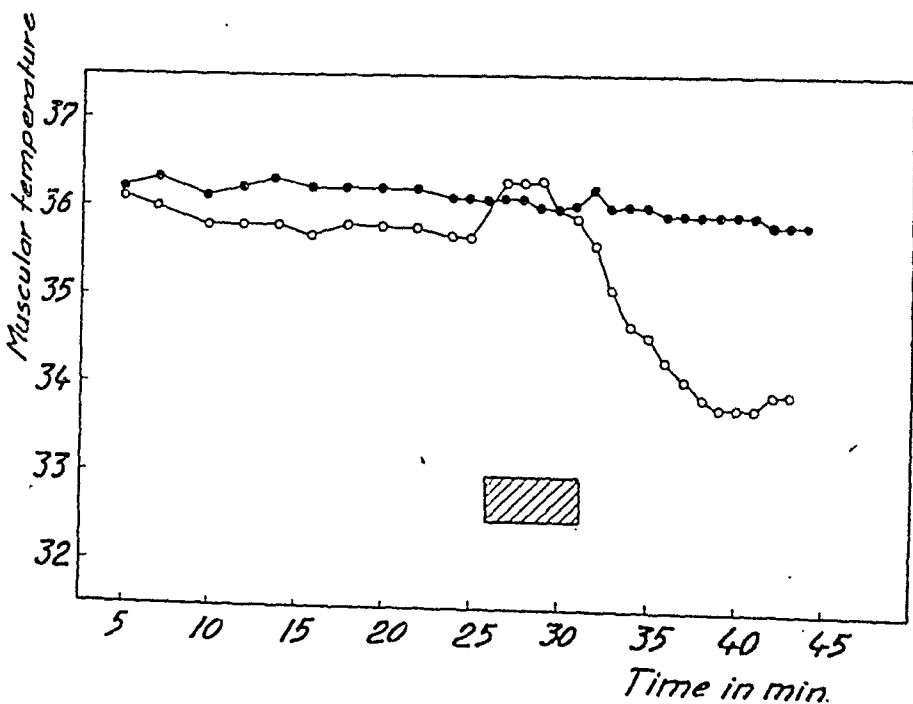



Fig. 2. Temperature of the right biceps brachii: —●—●—●—  
 » » the left » —○—○—○—  
 At  the skin covering the left biceps brachii is cooled with ice.

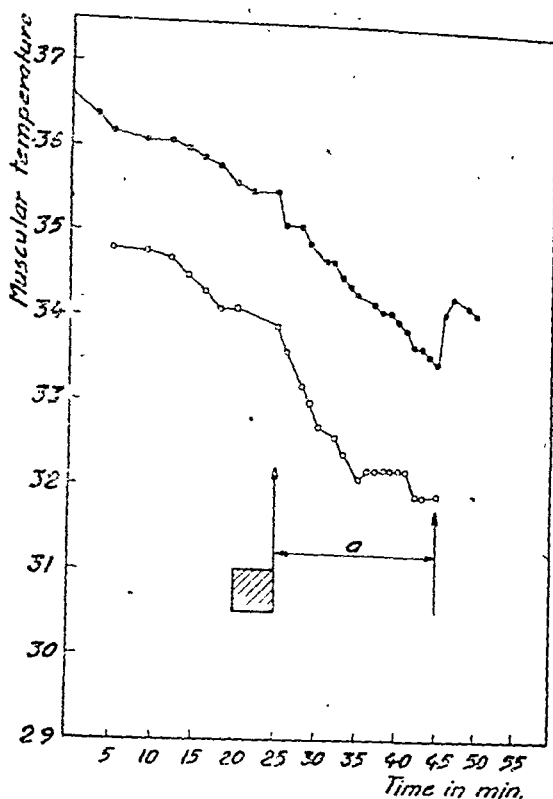



Fig. 3. Temperature of the right m. brachioradialis: —○—○—  
 » » the left » —●—●—

At  the skin covering the r. brachiorad. is cooled.

The bloodflow through the left arm is arrested between the arrows.

found that the fall in temperature following obstruction of the circulation was much slower and not so steep as the temperature decrease observed after cooling. (Fig. 3).

From these observations it can be concluded that the decline in muscular temperature following cooling cannot exclusively depend upon a contraction of the muscular vessels.

The dilatatory effect on the muscular vessels of adrenaline hydrochloride and amyl nitrite studied in a few persons, shows that the increase in muscular temperature produced by these agents never exceeds  $0.7^{\circ}\text{C.}$ , thus showing that the temperature effects produced by variations in the lumen of the muscular vessels are of far lesser order of magnitude than the temperature changes recorded after cooling the skin covering the muscle. It is therefore reasonable

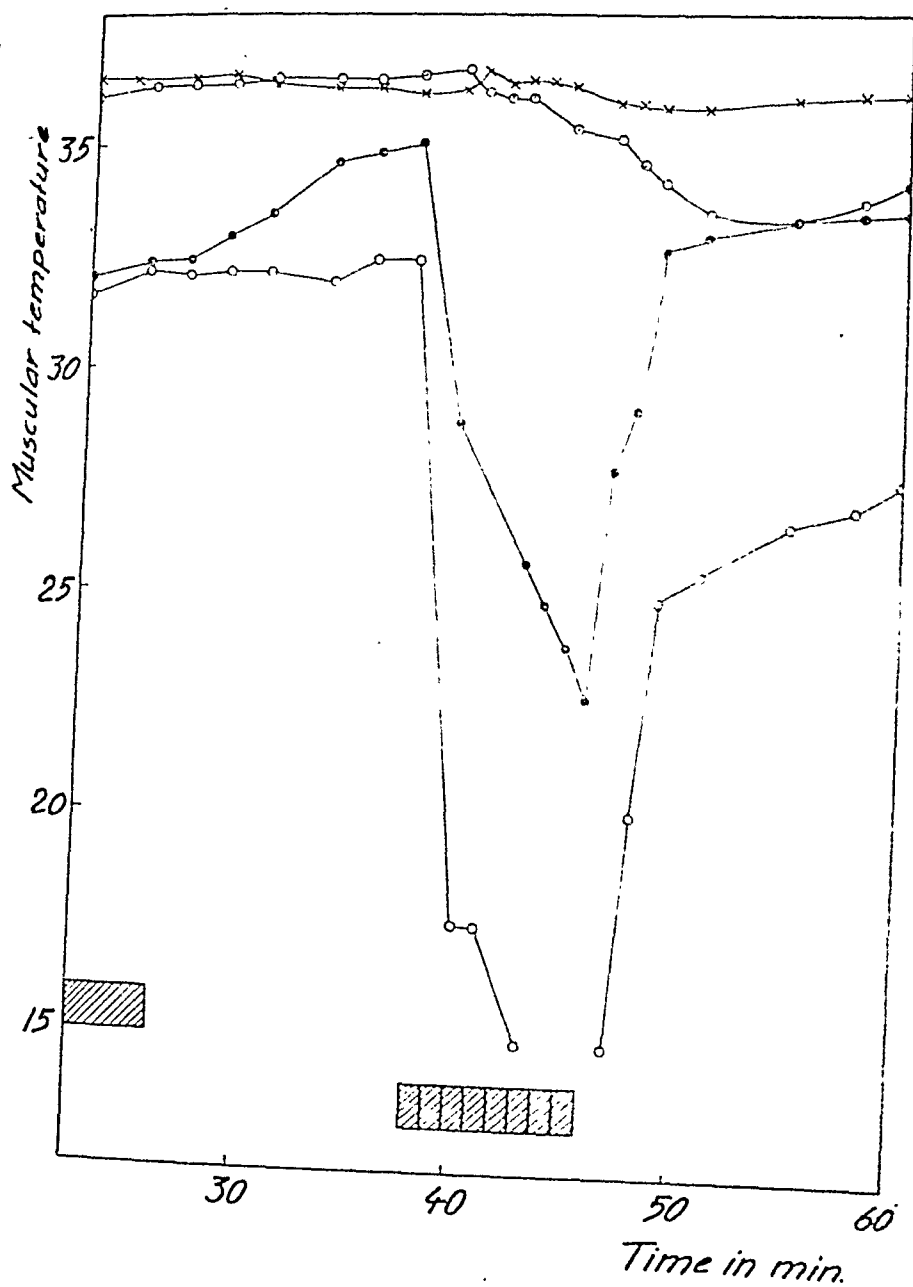




Fig. 4. A.S. Temperature of r. rectus femoris: —x—x—  
 » » l. » » —○—○—  
 » » skin cov. r. rect. fem.: —●—●—  
 » » » l. » » —○—○—  
 At  the skin covering the r. femur is infiltrated with 0.5 % novocain solution. At  the skin covering both muscles is cooled with ice.



to suppose that the most important factor in the decrease of muscular temperature caused by cooling must be a direct cooling of the muscular tissue. The skin and the subcutaneous tissues are not able to isolate and prevent a direct cooling of the muscles.

The possibility of a reflectory contraction of the muscular vessels due to the cooling of the skin, was excluded by another series of observations.

The receptors releasing the supposed reflex must be sought for in the skin. The skin to be cooled was accordingly anaesthetized by infiltrating it with 0.5 % novocain solution. The muscular temperatures beneath the anaesthetized part and at the corresponding spot in the symmetrical muscle were measured. The reaction of the muscular temperature on cooling both sides was observed. This arrangement had to be modified as the novocain infiltration produced a marked rise in the skin temperature which frustrated the cooling of the underlying muscle. (Fig. 4).

In the subsequent experiment the skin was infiltrated with 0.5 % novocain solution to which had been added 0.1 mg adrenalin hydrochloride. The symmetrical non-anaesthetized skin was infiltrated with 0.1 mg adrenalin hydrochloride dissolved in an equal amount of 0.9 % NaCl solution. Observations in 14 subjects made under these conditions did not show any difference in the cooling reactions on both sides (Fig. 5).

These observations thus prove conclusively that no reflectory constriction of the muscular vessels can be caused by stimulations of coldreceptors in the covering skin. The observations made with a pure 0.5 % novocain solution seems to indicate that paralysing the cutaneous vessels prevents the cooling of the subjacent muscle. No erythema was observed under these conditions.

The course of the temperature gradient: muscle-subcutaneous tissue-surface of the skin has been examined by measuring the skin temperature and the temperatures of the subcutaneous tissue and muscle. When the skin is exposed to room temperature only, the course of the gradient is linear, the gradients: muscle-subcutaneous tissue and subcutaneous tissue-surface of skin having the same inclinations and forming a continuous straight line.

If the surface of the skin is cooled to a temperature of  $0^{\circ}\text{C}$ , the inclination of the two gradients differs considerably thus forming

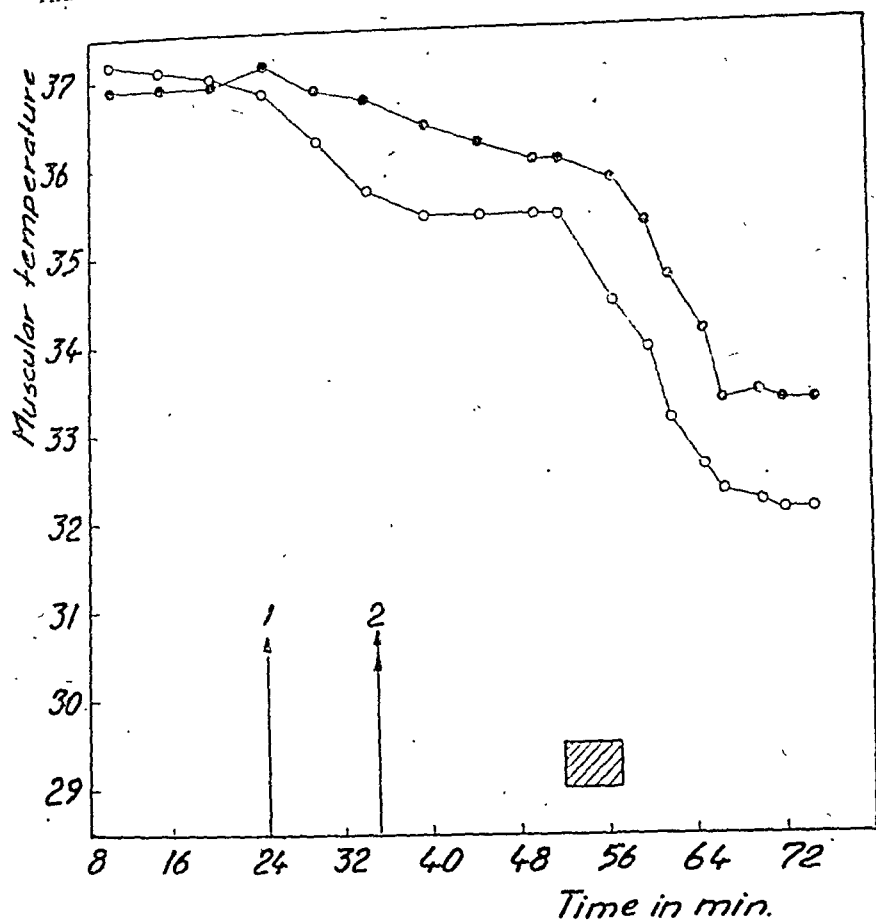



Fig. 5. A.S. Temperature of r. rect. femoris: —●—●—  
 » l. » » —○—○—

At 1. the skin covering the left rect. fem. is infiltrated with a 0.5 % novocain solution containing 0.1 mg adrenalinhydrochloride.

At 2. the skin covering the r. rectus femoris is infiltrated with an equal volume of 0.9 % NaCl-solution to which was added 0.1 mg adrenalin hydrochloride.

At  the skin covering the right muscle and the left muscle was cooled.

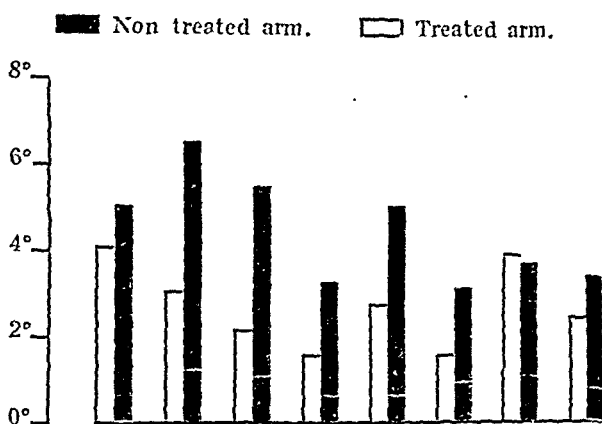
a broken line the part of which representing the gradient subcutaneous tissue-surface of skin showing much steeper incline than the part representing muscular tissue-subcutaneous tissue.

### Observations on skin irradiated with ultraviolet light.

It is a well known fact that ultraviolet rays, after a very short interval, produce an erythema, the intensity and duration of which depend upon the dosis given and the sensibility of the skin. After

the erythema has disappeared in the course of some days, non-visible changes in the reactivity of the cutaneous vessels may continue for a long time. Finsen (1899) has i.e. observed more vigorous reactivity of the vessels of the radiated skin compared to the non-radiated, persisting for 6 months. In 10 subjects we have studied the reaction to cold on the muscular temperature before and after ultraviolet radiation. The reactions have been compared with the untreated symmetrical side. The procedure was as follows:

Table 1.



Temperature fall after cooling the skin for 5 minutes. 8 subjects.  
1 week after the treatment with u. v. light.

The cooling reaction was observed in symmetrical muscles. The skin covering one of these was subsequently treated with ultraviolet light, the skin area radiated being 30 cm<sup>2</sup>. The distance from the mercury-quartz lamp being 10 cm, and the time of irradiation 2 ½ minutes (Fig. 6).

The ultraviolet light caused a marked erythema, which generally disappeared a week later. The cooling was repeated 7—9 days after the u.v. treatments. The temperature fall on the irradiated side was considerably less than on the untreated side. In two subjects the cooling experiments were repeated at intervals of a week for one month. The differences observed after this period were nearly of the same order of magnitude as those recorded a week after the exposure, even if an erythema had been present then Table 2.

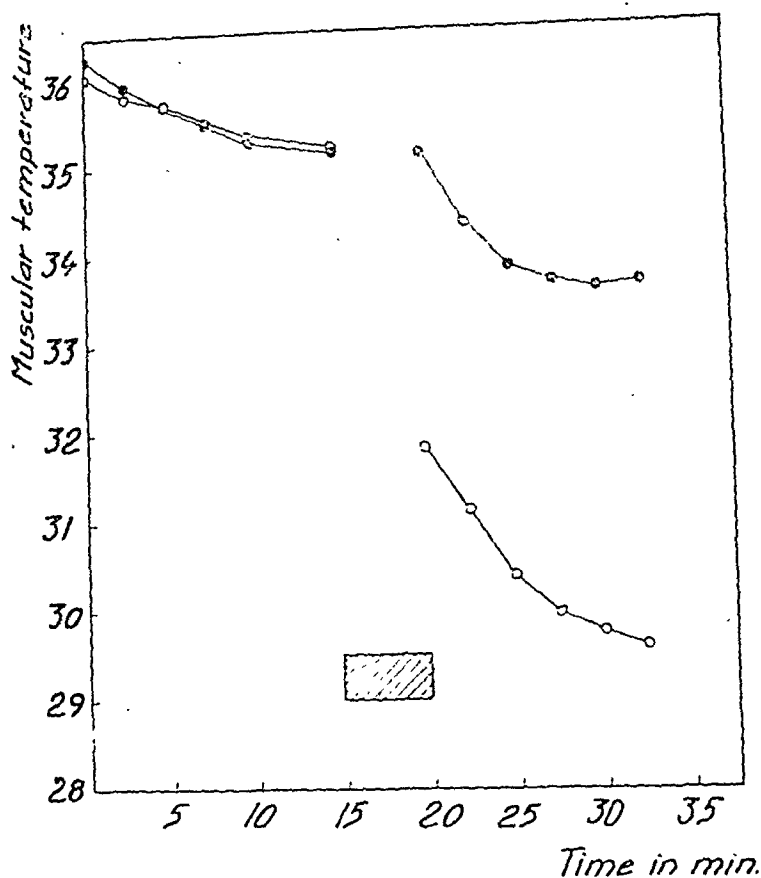



Fig. 6. temperature of the right biceps brachii: —○—○—  
 » » the left » —●—●—

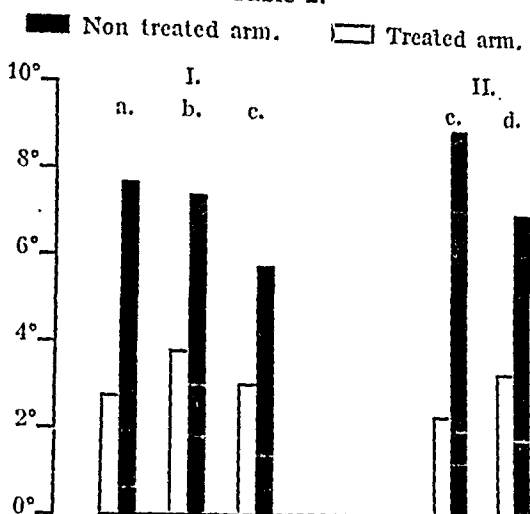
The skin of the left upperarm was exposed to a mercury quartzlamp a week preceeding the experiment shown in the figure.

At  both m bicipitis brachii were cooled with ice.

These observations indicate that the difference in the drop of muscular temperature due to cooling in the ultraviolet treated and untreated skin, depends upon differences in blood flow through the covering integuments, especially the skin. The skin being more able to compensate the increased heat loss after exposure to ultraviolet light.

The appearance of the skin when cooled, shows the following features. Immediately after cooling an erythema appears which disappears after a time which varies in different individuals. In some subjects this erythema is followed by an anemia of the skin which may persist for several hours. In these subjects a special deep

Table 2.



Temperature fall after cooling the skin for 5 minutes.

a = 1 week after the treatment with u. v. light.

b = 3 weeks " " " " " " " "

c = 6 " " " " " " " "

d = 7 " " " " " " " "

I = ♂ 21 years old

II = ♂ 73 " "

drop in muscular temperature could be observed. In the persons showing the greatest decline in muscular temperature a congelation of the 1. degree was seen. The congelation persisted for 4 days. This observation was confirmed in 4 experiments. It seems plausible that this abnormal reaction of the skin can cause pathological changes in muscular tissue.

This view is confirmed by the special liability of the subjects who responded with the deepest drop in muscular temperature when exposed to cold, to muscular discomfort after draughts.

### Summary.

1. The temperature of the biceps brachii has been recorded in 54 subjects. The changes in muscular temperature upon cooling the skin covering the muscle were recorded.

2. The same amount of cold applied to the skin produced a rather varied change in muscular temperature in different subjects.

In some cases the muscular temperature only dropped slightly while in others the muscular temperature showed a drop of  $10^{\circ}$ — $12^{\circ}$  C. The material did show a continuous transition from practically no decrease to the considerable decrease in muscular temperature.

3. Experiments indicate that the fall in muscular temperature is due to a direct cooling of the muscular tissue.

4. Experiments with cooling of moderate intensity indicate that the muscular vessels respond to cooling by a dilatation. At least an increased bloodflow through the muscles examined could be observed.

5. Reasons are given for believing that this is also the case when cooling of a more severe intensity is applied.

6. In experiments it has been conclusively proved that no reflectory constriction of the muscular vessels occurs when cold is applied to the skin covering the muscle investigated.

7. Evidence is brought forward to support the view that the magnitude of the temperature drop observed in muscles when cooling the covering skin depends upon the bloodflow through the covering skin and the subcutaneous tissue.

8. Observations on subjects whose skin had been treated with ultraviolet light support this view.

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